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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07H 19/167, A61K 31/70 — A1

(11) International Publication Number: WO 94/17090

(43) International Publication Date: 4 August 1994 (04.08.94)

(21) International Application Number: PCT/EP94/00145

(22) International Filing Date: 18 January 1994 (18.01.94)

(30) Priority Data:
9301000.7 20 January 1993 (20.01.93) GB

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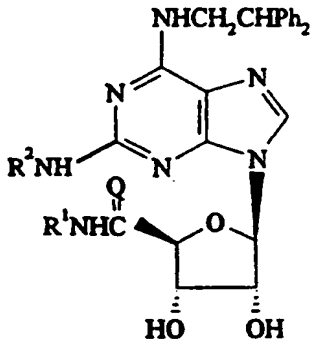
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: 2,6-DIAMINOPURINE DERIVATIVES

(57) Abstract

2,6-Diaminopurine-β-D-ribofuranuronamide derivatives are described having general formula (I) and salts and solvates thereof, wherein: R^1 is hydrogen, C_{3-8}cycloalkyl or C_{1-6}alkyl; R^2 is C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, Alk_1Y, $-(CHR^5)_m(Alk_2)_nZ$ or appropriately substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl, and Q is oxygen or sulphur. Compounds of formula (I) and their salts and solvates have use in medicine as anti-inflammatory agents, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.



(I)

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2,6-Diaminopurine Derivatives

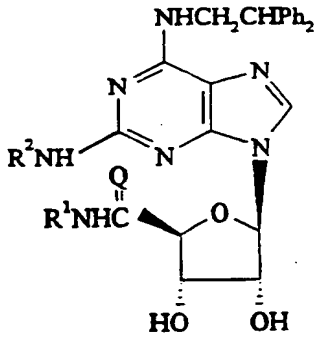
The present invention relates to therapeutically active 2,6-diaminopurine-β-D-ribofuranuronamide derivatives, processes for the manufacture of said compounds, pharmaceutical formulations containing said compounds and the use of said compounds in chemotherapy. In particular, we have found a group of novel compounds which are effective in treating inflammatory diseases.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by circulating leukocytes binding to and extravasion through vascular endothelium. Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by gene expression in vascular endothelium in response to a variety of inflammatory mediators.

The primary function of leukocytes is to defend the host from invading organisms such as bacteria and parasites. Once a tissue is injured or infected a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment and resolution are not adequately controlled and the inflammatory reaction causes tissue destruction.

We have now found a novel group of compounds with broad anti-inflammatory properties which inhibit leukocyte recruitment and activation. The compounds are therefore of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation. The compounds of the invention may also represent a safer alternative to corticosteroids in the treatment of inflammatory diseases, whose uses are severely limited by their side-effect profiles.

Thus, according to one aspect of this invention, we provide a compound of general formula (I)



(I)

and salts and solvates thereof, wherein:

R^1 represents a hydrogen atom or a C_{3-8}cycloalkyl or C_{1-6}alkyl group;

R^2 represents a group selected from

(i) C_{3-8}cycloalkyl

(ii) C_{3-8}cycloalkyl substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p is zero or 1 and R^3 is hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino)

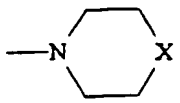
(iii) pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl)

(iv) pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl) and one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(v) C_{3-8}cycloalkylC_{1-6}alkyl

(vi) C_{3-8}cycloalkylC_{1-6}alkyl in which one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(vii) $-Alk_1Y$ where Alk_1 is a C_{2-6} alkylene group and Y is a group selected from C_{2-7}acylamino, guanidino, hydroxyl, NH_2, C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O, CH_2 or NR^4 in which R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl) and

(viii) $-(CHR^5)_m(Alk_2)_nZ$ where m and n each independently represent zero or 1 except that when m is 1 then n must also represent 1, R^5 is a hydrogen atom or a carboxy group or a group CH_2R^6 (where R^6 is C_{2-7}acylamino, guanidino, hydroxy, methoxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino), Alk_2 is a C_{1-5}alkylidene group and Z is a hydrogen atom or an optionally substituted aromatic ring selected from phenyl, pyridyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl and benzimidazolyl where the ring is optionally substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{1-6}alkyl, C_{2-7}acylamino, guanidino, carboxyethyl, hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino;

Q represents an oxygen or sulphur atom; and

Ph represents phenyl.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts such as acid addition salts derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates and maleates, and, if appropriate, inorganic base salts such as alkali metal salts, for example sodium salts. Other salts of the compounds of formula (I) include salts which are not physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. Examples of such salts include trifluoroacetates.

Examples of suitable solvates of the compounds of formula (I) include hydrates.

It will be appreciated that when R^2 in compounds of formula (I) contains one or more asymmetric carbon atoms the invention includes all diastereoisomers of compounds of formula (I) and mixtures thereof. Otherwise, the stereochemical configuration of compounds of the invention is as depicted in formula (I) above.

It is to be understood that all tautomeric forms of the compounds of formula (I) are included within the scope of this invention.

The cycloalkyl group within R^1 or R^2 may be a monocyclic or bridged cyclic ring. Particular examples of suitable cycloalkyl ring systems include C_{3-8} monocyclic cycloalkyl groups such as cyclopropyl, cyclopentyl and cyclohexyl. Within R^2 the C_{3-8} cycloalkyl group may particularly represent cyclopentyl or cyclohexyl.

The term 'aryl' as part of an arylC_{1-6}alkyl group may represent, for example, a phenyl group optionally substituted by one or more substituents (e.g. 1, 2 or 3 substituents) which may be the same or different and are selected from halogen, hydroxyl, C_{1-3}alkoxy and C_{1-3}alkyl.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group. Particular examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl.

The term 'alkylene' as part of a group means a straight or branched alkylene chain. Particular examples of suitable alkylene chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CHCH_3CH_2-$ and $-CH_2C(CH_3)_2CH_2-$.

When R^2 represents a group $-Alk_1Y$ the C_{2-6}alkylene group may particularly represent $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2C(CH_3)_2CH_2-$.

When R^2 represents a group $-(CHR^5)_m(Alk_2)_nZ$ the chain $-(CHR^5)_m(Alk_2)_n-$ may particularly represent a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^5CHCH_3CH_2-$ or $-CHR^5CH_2-$ (where R^5 is a group CH_2R^6 and R^6 is as defined previously).

The term 'C_{2-7}acylamino' within R^2 means a C_{2-7}alkanoylamino group wherein the C_{1-6}alkyl portion thereof is a straight or branched alkyl group as previously defined and may be optionally substituted by one or more halogen atoms such as fluorine. Examples of suitable C_{2-7}alkanoylamino groups within R^2 include acetamido and trifluoroacetamido.

Within Z, the term 'pyridyl' means a 2-, 3- or 4-pyridyl group; the term 'pyrimidinyl' means a 2-, 4- or 5-pyrimidinyl group; the term 'imidazolyl' means a 1-,2-,4- or 5-imidazolyl group; and the term 'triazolyl' means a 1, 2, 4-triazolyl group (e.g. 1, 2, 4-triazol-l-yl or 1, 2, 4-triazol-3-yl).

R^1 preferably represents a C_{1-3}alkyl group, especially ethyl.

Compounds of formula (I) in which Q represents an oxygen atom are generally preferred.

Compounds of formula (I) in which $R^1NHC(=Q)-$ represents ethylaminocarbonyl are particularly preferred.

A preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents a substituted cyclopentyl or cyclohexyl group wherein the ring is substituted by one or two groups, especially one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino, acetamido or trifluoroacetamido. Preferred substituents include hydroxy, dihydroxy, NH_2 and dimethylamino.

A further preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents a pyrrolidin-3-yl or piperidin-3-yl group in which the ring nitrogen atom is substituted by hydrogen, C_{1-3}alkyl (e.g. ethyl) or benzyl.

Another preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents $(CHR^5)_m(Alk_2)_nZ$ where R^5, m and n are as defined previously and Z is an optionally substituted imidazolyl group. Particularly preferred are those compounds in which $-(CH_2R^5)_m(Alk_2)_n-$ represents $-CH_2CH_2-$.

It is to be understood that the present invention covers all combinations of particular and preferred groups referred to hereinabove.

Specific compounds of the present invention include:

(1S-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

(1R-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

[1S-(1α,2β,3β)]-1-deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

[cis-(+/-)]1-[2-[(3-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;

(trans)-1-[2-[(2-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, isomer 1;

[1S-trans]-1-[2-[(3-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;

[1R-trans]-1-[2-[(3-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;

[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-[(trifluoroacetyl)amino]cyclopentyl]amino]-N-ethyl-9H-purin-9-yl]-β-D-ribofuranuronamide;

1-deoxy-1-[6-[(2,2-diph nylethyl)amino]-2-[[2-(1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(cis)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-N-ethyl-1-[2-[(3-hydroxypropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-β-D-ribofuranuronamide;
1-[2-[(4-aminophenyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[2-[[4-(dimethylamino)phenyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(1α,2β,5β)-1-deoxy-1-[2-[[2,5-dihydroxycyclopentyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-(4-hydroxy-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(N-ethylpiperidin-3-yl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-piperidinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(4-morpholinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-pyridinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(pyrrolidin-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-(3-pyridinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-(methyl)propyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[cis-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-deoxy-1-[2-[[2-(N,N-dimethylamino)ethyl]amino]-6-[(2,2-diph nylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[2-[[3-(N,N-dimethylamino)propyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(1α,3β,4β)-1-deoxy-1-[2-[(3,4-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[(1S)-trans]-1-deoxy-1-[2-[(3-N,N-dimethylamino)cyclopentylamino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(3R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(3R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(1-ethyl-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(1-ethyl-4-piperidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(trans)-1-[2-[(4-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
[(1α,2β,3β)-(+/-)]-1-[2-[(3-acetylamino-2-hydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
(1R-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino]-N-ethyl-9H-purin-9-yl]-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-imidazol-2-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-(1H-imidazol-4-yl)propyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-1,2,4-triazol-3-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(trans)-1-deoxy-1-[2-[(4-N,N-dimethylaminocyclohexyl)amino]6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-methyl-1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[2-[[2-[(aminoiminomethyl)amino]ethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[2-[[3-[(aminoiminomethyl)amino]propyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-[2-[[(6-amino-2-pyridinyl)methyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
and physiologically acceptable salts and solvates thereof.

Particular compounds of the present invention include:
(1S-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[1S-(1α,2β,3β)]-1-deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[(1S)-trans]-1-deoxy-1-[2-[(3-N,N-dimethylamino)cyclopentylamino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(trans)-1-[2-[(4-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino]-N-ethyl-9H-purin-9-yl]-β-D-ribofuranuronamide;
(trans)-1-deoxy-1-[2-[(4-N,N-dimethylaminocyclohexyl)amino]6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-methyl-1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
and physiologically acceptable salts and solvates thereof.

A particularly preferred compound of formula (I) is:
(trans)-1-[2-[(4-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide; and physiologically acceptable salts and solvates thereof, including the hydrochloride salt.

The potential for compounds of formula (I) to inhibit leukocyte function may be demonstrated, for example, by their ability to inhibit superoxide (O_2^-) generation from neutrophils stimulated with chemoattractants such as N-formylmethionyl-leucyl-phenylalanine (fMLP). Accordingly, compounds of

formula (I) are of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis (including chronic bronchitis), cystic fibrosis, asthma (including allergen-induced asthmatic reactions), emphysema, rhinitis and septic shock. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), Helicobacter-pylori induced gastritis and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, and non-steroidal anti-inflammatory drug-induced gastropathy. Furthermore, compounds of the invention may be used to treat skin diseases such as psoriasis, allergic dermatitis and hypersensitivity reactions.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiac conditions such as peripheral vascular disease, post-ischaemic reperfusion injury and idiopathic hypereosinophilic syndrome.

Compounds of the invention which inhibit lymphocyte function also have use in the treatment of auto-immune diseases such as rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof

for the manufacture of a medicament for the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition who is susceptible to leukocyte-induced tissue damage, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable carriers or excipients.

The compounds according to the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration, preferably for parenteral or topical (e.g. by aerosol) administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl

or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator, solutions for nebulisation or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluorethane, carbon dioxide or other suitable gas.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges of for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents such as corticosteroids or NSAIDs.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent, for example an anti-inflammatory agent such as a corticosteroid or NSAID.

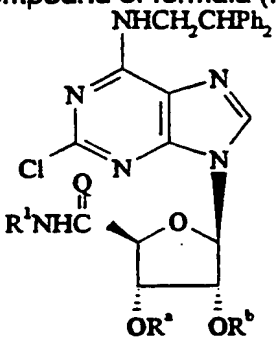
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Compounds of the inv ntion may conveniently be administered in amounts of, for example, 0.01 to 500mg/kg body weight, preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention. In the following procedures, the groups R^1, R^2 and Q are as defined for compounds of formula (I) unless otherwise stated.

Thus, according to first process (A), a compound of formula (I) may be prepared by treating a compound of formula (II)



(II)

(wherein R^a and R^b each represent a hydrogen atom or together form an alkylidene group such as isopropylidene) with an amine $R^{2a}NH_2$ (wherein R^{2a} is a group R^2 or is a protected derivative thereof), followed, where necessary, by the removal of any protecting groups present.

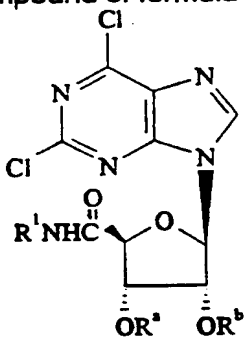
The displacement reaction to introduce the amine moiety may be carried out by heating the reagents at a temperature in the range of 50^0 to 150^0C optionally in the presence of a solvent such as dimethylsulphoxide.

A compound of formula (II) in which Q represents a sulphur atom may be prepared from a compound of formula (II) in which Q represents an oxygen atom and R^a and R^b together form an alkylidene group such as isopropylidene by thianation followed, if appropriate, by the removal of the alkylidene group.

The thianation reaction may be conveniently effected using known thianation agents such as hydrogen sulphide, phosphorus pentasulphide or Lawesson's reagent (p-methoxyphenylthiophosphine sulphide dimer). The reaction may be carried out in a known manner. For example when hydrogen sulphide is used an acid such as hydrochloric acid may conveniently be added in catalytic

amounts and the reaction carried out in a polar solvent such as acetic acid or ethanol. When using Lawesson's reagent, the reaction may conveniently be carried out in a dry solvent such as toluene or methylene chloride.

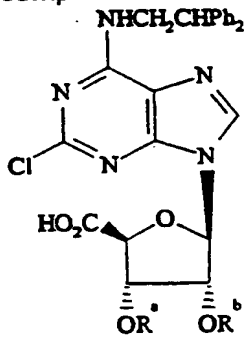
A compound of formula (II) in which Q represents an oxygen atom may be prepared by treating a compound of formula (III)



(III)

(wherein R^a and R^b are as defined previously) with 2,2-diphenylethylamine, preferably in the presence of a base such as an amine base (e.g. diisopropylethylamine) and in a solvent such as an alcohol (e.g. isopropanol) at an elevated temperature (e.g. reflux), followed if desired by removing any protecting groups present.

A compound of formula (II) in which Q represents an oxygen atom may also be prepared by treating a compound of formula (IV)



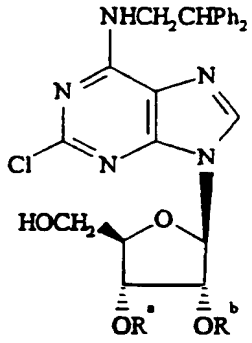
(IV)

(wherein R^a and R^b are as defined previously) or an active derivative thereof such as the corresponding acid halide with an amine R^1NH_2, followed if desired by removing any protecting groups present.

The amination reaction may be effected in known manner, for example by adding the amine in a solvent such as a halogenated hydrocarbon (e.g. methylene chloride) at about 0^0 to 20^0C to the compound (IV) or, more particularly, the corresponding acid chloride. The acid chloride may be

prepared by treating compound (IV) with thionyl chloride, conveniently at an elevated temperature.

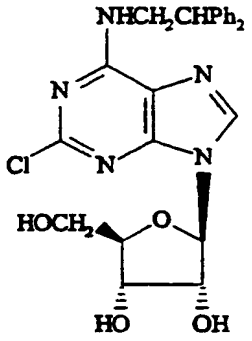
A compound of formula (IV) may be prepared by oxidising a compound of formula (V)



(V)

or a salt thereof (wherein R^a and R^b together form an alkylidene group such as isopropylidene), followed if desired by removing the alkylidene group. The oxidation reaction may be effected in known manner using an oxidising agent such as potassium permanganate or pyridinium dichromate.

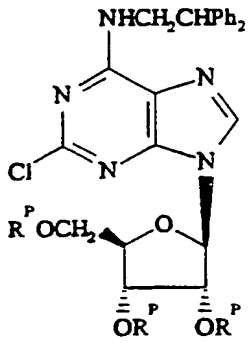
A compound of formula (V) or a salt thereof may be prepared by treating a compound of formula (VI)



(VI)

with a ketone such as acetone and/or with 2,2-dimethoxypropane in the presence of an acid, for example p-toluenesulphonic acid, conveniently at about room temperature.

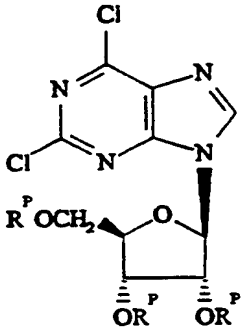
A compound of formula (VI) may be prepared by deprotecting a compound of formula (VII)



(VII)

(wherein R^P is a suitable hydroxyl protecting group). Suitable methods of deprotection are described hereinafter.

A compound of formula (VII) may be prepared by treating a compound of formula (VIII)



(VIII)

(wherein R^P is as defined previously) with 2,2-diphenylethylamine under the conditions described previously for preparing compounds of formula (II) from compounds of formula (III).

The compounds of formulae (III) and (VIII) are either known compounds or may be prepared by methods analogous to those described in the art for preparing the known compounds of formulae (III) and (VIII).

The amines $R^{2a}NH_2$ are either known in the art or may be prepared by the methods described in the Examples Section hereinafter or by methods analogous to such methods hereinafter.

Compounds of formulae (II) and (IV) are novel intermediates and represent further aspects of the present invention. Compounds of formula (II) in which R^a and R^b represent hydrogen atoms are also active compounds in their own right and constitute a further particular aspect of the present invention.

It will be appreciated that in addition to 2',3'-diol groups, groups present within R^2 may need to be protected, and deprotection may be required as an

intermediate or final st p to yield the desired compound. Thus, according to another general process (B), a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) to reaction to remove the protecting group or groups. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) or sulphonyl (e.g. allysulphonyl or tosyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1991). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride. Carboxyl protecting groups may conveniently be represented by appropriate hydroxyl protecting groups above with deprotection effected according to the methods described above. An example of such a group is an alkyl (e.g. methyl or t-butyl) group which can be removed by acid hydrolysis (e.g. using trifluoroacetic or hydrochloric acid) or an aralkyl (e.g. benzyl) group which can be removed by catalytic hydrogenolysis.

Particularly suitable hydroxyl protecting groups represented by R^P include acyl groups such as acetyl or benzoyl. An alkylidene protecting group may conveniently be removed by acid-catalysed hydrolysis, for example using trifluoroacetic, sulphuric or hydrochloric acid.

Compounds of formula (I) may also be prepared from other compounds of formula (I) or protected derivatives thereof using conventional interconversion procedures, including N-acylation, N-debenzylation and oxidation of a hydroxyl group to a ketone, followed, if necessary, by the removal of any protecting groups present.

Individual isomers of formula (I) may either be prepared from starting materials having the desired stereochemistry or by epimerisation, resolution or chromatography (e.g. HPLC separation) at an appropriate stage in the synthesis of the required compounds of formula (I) using conventional means.

When it is desired to prepare an acid addition salt of a compound of formula (I) the product of the above procedure may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods.

Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) in the form of a free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g. ethyl acetate) or an alcohol (e.g. methanol, ethanol or isopropanol).

Inorganic basic salts may be prepared by reacting the free base of a compound of formula (I) using conventional methods.

Solvates (e.g. hydrates) of a compound of formula (I) may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C. Hereinafter the term DMSO means dimethylsulphoxide.

EXAMPLES

General

Where products were purified by column chromatography, 'silica' refers to silica gel for chromatography, 0.063 to 0.20mm mesh (e.g. Merck Art 7735); 'flash silica' refers to silica gel for chromatography, 0.040 to 0.063mm mesh (e.g. Merck Art 9385). In this latter case column elution was accelerated by an applied pressure of nitrogen at up to 5 p.s.i.

Where products were purified by preparative HPLC, this was carried out on a C18-reversed-phase column (1" Dynamax), eluting with a gradient of acetonitrile (containing 0.1% trifluoroacetic acid) in water (containing 0.1% trifluoroacetic

acid) and the compounds isolated as their trifluoroacetate salts unless otherwise specified.

PREPARATION 1

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-triacetate

A solution of 2,6-dichloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine[1] (6.68g,14.9mmol) in 2-propanol (300ml) was stirred and heated at reflux with 2,2-diphenylethylamine (4.3g,21.8mmol) in the presence of diisopropylethylamine (3.8ml) for 3.5h. The cooled mixture was reduced in volume by evaporation in vacuo and the residue was diluted with ethyl acetate (200ml). This mixture was washed with water (100ml), 10% citric acid solution (2x100ml) and water (100ml) then dried ($MgSO_4$) and evaporated to give the title compound (9.01g) as a pale yellow froth. A sample (500 mg) was purified by column chromatography on flash silica eluting with ethyl acetate:cyclohexane (1:2). The product (0.34g) was obtained as a white froth $[\alpha]_D$ -20° ($CHCl_3$ c=1%).

1. M.J.Robins and B.Uznanski, Canad.J.Chem., 1981, 59(17), 2608.

PREPARATION 2

2-Chloro-N-(2,2-diphenylethyl)-adenosine

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-triacetate (2.0g,3.29mmol) was dissolved in methanol (120ml) and the solution was stirred at room temperature with 2M aqueous sodium carbonate solution (10ml). After 2h the mixture was diluted with water (350ml) and extracted with ethyl acetate (2x100ml). The extract was washed with water (100ml) and dried ($MgSO_4$) then evaporated to leave a froth (1.42g). A sample (0.42g) was purified by column chromatography on flash silica eluting with ethyl acetate:cyclohexane (3:1). Evaporation of appropriate fractions gave an oil which was treated with ether (20 ml) to give a solid, which was collected by filtration, washed with ether and dried in vacuo to give the title compound (0.177g) as a solid $[\alpha]_D$ -39° ($CHCl_3$ c=1%).

PREPARATION 3

2-Chloro-N-(2,2-diphenylethyl)-2,3-O-(1-methylethylidene)-adenosine toluene-4-sulphonate salt

Toluene-4-sulphonic acid (7.0g,37mmol) was added to a stirred solution of 2-chloro-N-(2,2-diphenylethyl)-adenosine (6.85g,14mmol) in acetone (300ml) and 2,2-dimethoxypropane (90ml). After a few minutes a precipitate formed which dissolved within 0.5h. The reaction was stirred for 3 days and the precipitate formed was collected by filtration and washed with acetone (50ml) and dried to give the title compound (4.64g) $[\alpha]_D$ -38° (1,4-dioxan c=1%). A second crop (2.7g) was obtained from the mother liquors.

PREPARATION 4

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-2,3-O-(1-methylethylidene)-β-D-ribofuranuronic acid

A solution of 2-chloro-N-(2,2-diphenylethyl)-2,3-O-(1-methylethylidene)-adenosine toluene-4-sulphonate salt (6.94g,10mmol) in 1,4-dioxan (200ml) was added to a cold (4°C) solution of potassium permanganate (8.85g,56.1mmol) and potassium hydroxide (2.71g,48.4mmol) in water (200ml) keeping the temperature below 10°C. On complete addition the mixture was stirred for 3.5h between 5°C and room temperature. A 5% aqueous solution of sodium metabisulphite was added in portions until all colouration had been discharged. The pH was then adjusted to pH 3 with concentrated hydrochloric acid and the mixture was extracted with ethyl acetate (3x200ml). The extract was washed with water (200ml) and dried ($MgSO_4$) and evaporated to leave a waxy solid (5.45g) which was dried in vacuo. The majority of this solid (4.1g) was stirred with ether (100ml) and 5% aqueous sodium bicarbonate solution (100ml) until solution was obtained. The aqueous phase was washed with ether (2x100ml) then brought to pH3 with 10% citric acid solution to give a precipitate which was collected by filtration, washed with water (100ml) and dried. The resulting solid (6.1g) was stirred with water (500ml) for 2h then collected by filtration, washed with water (50ml) and dried in vacuo over phosphorus pentoxide to give the title compound (3.52g) $[\alpha]_D$ +53° ($CHCl_3$ c=1%).

PREPARATION 5

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-2,3-O-(1-methylethylidene)-β-D-ribofuranuronic acid (3.3g,6.16mmol) in thionyl chloride (10ml) was heated at 70°C for 1.5h. The mixture was evaporated to leave a pale brown froth which was azeotroped with toluene twice. The resulting froth was dissolved in dichloromethane (50ml) and the solution was cooled to 5°C. A solution of ethylamine (6ml) in dichloromethane (20ml) was added in portions and the mixture was left at 5°C for 30 min then poured into water (100ml). The aqueous phase was extracted with dichloromethane (3x50ml), the extract was washed with water and dried ($MgSO_4$) then evaporated to leave a froth (3.37g) which was purified by column chromatography on flash silica eluting with ethyl acetate:cyclohexane (1:1) to give the title compound (2.74g) as a pale yellow froth $[\alpha]_D$ -18.9° ($CHCl_3$ c=0.9%).

PREPARATION 6

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-tribenzoate

A mixture of 2,6-dichloro-9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-9H-purine[1] (67.69g), 2,2-diphenylethylamine (27.67g) and diisopropylethylamine (75.5g) in 2-propanol (2200ml) was heated under reflux for 2.5h. The cooled mixture was evaporated, and the residual orange foam purified on flash silica (1.5 kg) eluting with ethyl acetate:cyclohexane (1:2) to yield the title compound (71.2g) as a pale brown foam, nmr(δ,$CDCl_3$) 4.2 to 4.4 and 4.6 to 4.95 (2m,6H), 5.97 (br.s,1H),6.14 (q,2H), 6.43 (d,1H), 7.15 to 7.65 (m, ca 19H), 7.79 (s,1H), 7.9 to 8.15 (m,6H).

1. K.Imai, et al., Chem. Pharm. Bull., 1966, 14, 1377.

PREPARATION 7

2-Chloro-N-(2,2-diphenylethyl)-adenosine

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-tribenzoate (71.2g) in methanol (980ml) was treated with potassium carbonate (52.1g). The suspension was stirred at 22°C for 2h. It was then acidified to pH 8 with concentrated hydrochloric acid, evaporated and purified on flash silica (2kg) eluting with dichloromethane:ethanol:0.880 ammonia (90:10:1) to give the title compound (40.2g) as a white solid, nmr(δ,DMSO-d_6) 3.58 (m,1H), 3.65 (m,1H),

3.84 (br.s,1H), 4.0 to 4.2 and 4.4 to 4.65 (2m,5H), 5.04 (t,1H), 5.22 (d,1H), 5.48 (d,1H), 5.82 (m,1H), 7.1 to 7.4 (m,10H), 8.33 (s,1H), 8.42 (t,1H).

PREPARATION 8

2-Chloro-N-(2,2-diphenylethyl)-2,3-O-(1-methylethylidene)-adenosine

2-Chloro-N-(2,2-diphenylethyl)-adenosine (40g) in acetone (970ml) was treated with 2,2-dimethoxypropane (49ml) and toluene-4-sulphonic acid (4.97g). The mixture was stirred at ca 22°C for 67h, then the slurry was evaporated and chromatographed on flash silica eluting with dichloromethane:methanol (19:1) to give the title compound (39.6g) as a white solid. A portion (1.5g) was recrystallised from ethyl acetate to give an analytically pure sample, 1.27g, m.p. 185 to 187°, $[\alpha]_D$ -86°(c,0.8%, $CHCl_3$).

PREPARATION 9

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

1-(2,6-Dichloro-9H-purin-9-yl)-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide[1] (5.66g, 14.07mmol) was heated at reflux in 2-propanol (300ml) with 2,2-diphenylethylamine (3.62g, 18.3mmol) in the presence of N,N-diisopropylethylamine (13.2ml) for 6h. The cooled solution was evaporated to a brown foam which was purified on silica eluting with ethyl acetate to give the title compound (7.31g) as a pale yellow foam, nmr(δ,DMSO-d6) 0.62(t,3H), 1.34(s,3H), 1.53(s,3H), 2.82(m,2H), 4.05(m,1.5H), 4.54(m,2.5H), 5.40(m,2H), 6.18(s,1H), 7.1 to 7.4(m,10H), 7.50(t,1H), 8.22(s,1H), 8.40(m,1H).

1. R.R.Schmidt et al., Chem.Ber., 1980, 113, 2891.

PREPARATION 10

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (2.02g) was treated with trifluoroacetic acid (10ml) and water (1.1ml), and the resulting solution was stirred at 20°C for 2h. The mixture was evaporated and the residue was treated with sodium hydrogen carbonate (3.75g) and ethanol (30ml) and stirred for 1h. The mixture was filtered and the solid was washed with ethanol. The total filtrate

and washings were vaporated and the r sidue was purified on flash silica eluting with ethyl acetate:methanol (19:1) to give the title compound (1.96g) as a white solid, nmr(δ,DMSO-d6) 1.05(t,3H), 3.22(m,2H), 4.0 to 4.2(m,2.5H), 4.30(m,1H), 4.45 to 4.65(m,2.5H), 5.58(d,1H), 5.72(d,1H), 5.90(d,1H), 7.14 to 7.40(m,10H), 8.36(t,1H), 8.43(s,1H), 8.52(t,1H).

PREPARATION 11

[cis-(+/-)]-[3-[(Methylsulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester

Methanesulphonyl chloride (0.163ml,2.1mmol) was added to a stirred mixture of [cis-(+/-)]-(3-hydroxycyclopentyl)carbamic acid phenylmethyl ester[1] (0.47g,2mmol) and triethylamine (0.293ml,2mmol) in acetone (10ml). After 2h more reagents as above were added and the reaction was left for a further 1h. Water (70ml) and ethyl acetate (70ml) were added and the organic phase was washed with water (20ml), dried ($MgSO_4$) and evaporated to leave a solid (0.71g) which was purified by column chromatography on flash silica eluting with 50% ethyl acetate in cyclohexane to give the title compound (0.532g), m.p.84-86°C (from ether).

1. Published European Patent Application EP-A-322242.

PREPARATION 12

[trans-(+/-)]-[3-(N,N-Dimethylamino)cyclopentyl]carbamic acid phenylmethyl ester

A solution of [cis-(+/-)]-[3-[(methylsulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester (2g,6.38mmol) in 33% dimethylamine in ethanol (30ml) was heated at reflux for 4h. The cooled mixture was diluted with water (250ml) and extracted into ethyl acetate (3x70ml). The extract was dried ($MgSO_4$) and evaporated to leave an oil which crystallised from ether/cyclohexane to give the title compound (1.28g) m.p. 85-86°C.

PREPARATION 13

[trans-(+/-)]-3-(N,N-Dimethylamino)cyclopentylamine

A solution of [trans-(+/-)]-[3-(N,N-dimethylamino)cyclopentyl]carbamic acid phenylmethyl ester (1.4g,5.34mmol) in tetrahydrofuran (100ml) was hydrogenated over 10% palladium-on-carbon (0.17g) for 3 days. The catalyst

was removed by filtration, washed with tetrahydrofuran (20ml) and the combined organic phases were evaporated with a stream of nitrogen to leave the title compound (0.412g) as an oil, nmr(δ,$CDCl_3$) includes 1.25-1.65(m,3H), 1.7-1.85(m,1H), 1.85-2.1(m, 2H), 2.25(s,6H), 2.65(m, 1H), 3.48(m, 1H).

PREPARATION 14

[trans-(+/-)]-(3-Azidocyclopentyl)carbamic acid phenylmethyl ester

A solution of sodium azide (0.5g, 7.69mmol) in water (2ml) was added to a solution of [cis-(+/-)]-[3-[(methanesulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester (1.74g, 5.55mmol) in dimethylformamide (12ml) and the mixture was heated at 100°C for 0.5h.The cooled reaction mixture was diluted with water (150ml) and extracted into ethyl acetate (3x50ml). The extract was washed with water (50ml), dried ($MgSO_4$) and evaporated to leave the title compound (1.41g) as an oil which solidified on drying, nmr(δ,$CDCl_3$) includes 1.4-1.55(m,1H), 1.6-1.85(m,2H), 1.95-2.3(m,3H), 4.05(m,1H), 4.17(m,1H), 4.72(bs,1H), 5.1(s,2H), 7.45(s,5H).

PREPARATION 15

[trans-(+/-)]-(3-Aminocyclopentyl)carbamic acid phenylmethyl ester

A solution of [trans-(+/-)]-(3-azidocyclopentyl)carbamic acid phenylmethyl ester (4.65g,0.0179mmol) in ethanol (230ml) was hydrogenated over 10% palladium-on-carbon (0.5g) by bubbling hydrogen through the stirred solution for 40min. The mixture was filtered through celite and the pad was washed with ethanol (50ml). The combined ethanolic solution was evaporated to leave an oil (4.2g) which was partitioned between 2M hydrochloric acid (50ml) and ethyl acetate (50ml). The organic phase was extracted with 2M hydrochloric acid (2x20ml) and the combined aqueous phase was brought to pH 8 with sodium carbonate solution and extracted with ethyl acetate (3x70ml). The extract was dried ($MgSO_4$) and evaporated to leave the title compound (0.32g) as a solid, nmr(δ,$CDCl_3$) includes 1.25-1.45(m,4H), 1.75(t,2H), 1.9-2.1(m,1H), 2.1-2.3(m,1H), 3.47(m,1H), 4.2(m,1H), 4.72(bs,1H), 5.1(s,2H), 7.47(s,5H).

PREPARATION 16

[trans-(+/-)]-[3-[(Methylsulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester

Methanesulphonyl chloride (1.42ml,18.35mmol) was add d to a stirred solution of [trans-(+/-)]-(3-hydroxycyclopentyl)carbamic acid phenylmethyl ester[1] (2.16g,9.19mmol) and triethylamine (2.54ml, 18.35mmol) in acetone (100ml). The mixture was stirred for 2h then diluted with water (500ml) and extracted into ethyl acetate (3x100ml). The extract was washed with water (100ml), dried ($MgSO_4$) and evaporated to leave the title compound (2.75g) as a solid, nmr(δ,$CDCl_3$) includes 1.45-1.6(m,1H), 1.77-1.9(m,1H), 1.9-2.1(m,1H), 2.1-2.3(m,2H), 2.3-2.45(m,1H), 3.0(s,3H), 4.25(m,1H), 4.73(bs,1H), 5.1(s,2H), 5.2(m,1H), 7.35(s,5H).

1. Published European Patent Application EP-A-322242.

PREPARATION 17

[cis-(+/-)]-(3-Azidocyclopentyl)carbamic acid phenylmethyl ester

Sodium azide (0.74g, 10.4mmol) was dissolved in water (4ml) and the solution was added to a solution of [trans-(+/-)]-[3-[(methylsulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester (2.35g, 7.25mmol) in dimethylformamide (15ml). The mixture was heated at 100°C for 2h, cooled and partitioned between ethyl acetate (50ml) and water (50ml). The aqueous phase was extracted with ethyl acetate (2x50ml) and the combined extract was washed with water (2x50ml), dried ($MgSO_4$) and evaporated to leave the title compound (1.92g) as an oil, nmr(δ,$CDCl_3$) includes 1.55-1.7(m,2H), 1.85(m,2H), 2.0-2.27(m,2H), 4.05(m,1H), 4.17(m,1H), 5.0(m,1H), 5.1(s,2H), 7.35(s,5H).

PREPARATION 18

[cis-(+/-)]-(3-Aminocyclopentyl)carbamic acid phenylmethyl ester

A solution of [cis-(+/-)]-(3-azidocyclopentyl)carbamic acid phenylmethyl ester (1.46g, 5.61mmol) in ethanol (60ml) was hydrogenated over 10% palladium-on-carbon (0.2g) by bubbling hydrogen through the solution for 30min. The catalyst was removed by filtration, washed with ethanol (20ml) and the combined organic solution was evaporated to leave an oil (1.41g). A portion (1g) was partitioned between 2M hydrochloric acid (5ml) and ethyl acetate (10ml). Water was added and the aqueous phase was washed with ethyl acetate (2x10ml), brought to pH 9 with sodium carbonate solution and extracted with ethyl acetate (3x25ml). The extract was washed with water (2x20ml), dried ($MgSO_4$) and evaporated to

leave the title compound (0.37g) as an oil, nmr(δ,$CDCl_3$) includes 1.25-1.55(m,2H), 1.65-1.95(m,2H), 1.95-2.1(m,2H), 3.52(m,1H), 4.15(m,1H), 5.1(s,2H), 5.33(m,1H), 7.35-7.45(m,5H).

PREPARATION 19

2,5-Dihydro-1H-pyrrole-1-carboxylic acid 1,1-dimethylethyl ester

Di-t-butyl pyrocarbonate (84.2g, 0.386mole) was added to an ice-cold solution of 70% pure 3-pyrroline (25g, 0.253mole) in 1,4-dioxan (150ml). After 3 days the mixture was diluted with ethyl acetate (200ml) and washed with water (5x200ml). The aqueous phase was extracted with ethyl acetate (100ml) and the combined organic solution was washed with water (100ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluting with 30% ethyl acetate in cyclohexane to give the title compound (48.6g) as an oil, nmr(δ,$CDCl_3$) includes 1.45(s,9H), 4.12(dd, 4H), 5.77(m,2H).

PREPARATION 20

3-[(1,1-Dimethylethoxy)carbonyl]-6-oxa-3-azabicyclo[3.1.0]hexane

80% m-Chloroperbenzoic acid (3.9g, 0.0226mole) was added to a solution of 2,5-dihydro-1H-pyrrole-1-carboxylic acid 1,1-dimethylethyl ester (3.55g, 0.021mole) in dichloromethane (70ml) and the mixture was stirred for 24h when more peracid (0.27g,0.00156mole) was added and the stirring continued for a further 4h. Ethyl acetate was added and the mixture was washed with 10% sodium carbonate solution. The aqueous phase was extracted with ethyl acetate (50ml) and the combined organic solution washed with water, dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluting with 30% ethyl acetate in cyclohexane to give the title compound (1.52g) as an oil, nmr(δ,$CDCl_3$) includes 1.45(s,9H), 3.42(dd,2H), 3.67(s,2H), 3.78(dd,2H).

PREPARATION 21

[trans-(+/-)]-3-Hydroxy-4-[(phenylmethyl)amino]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester

A solution of 3-[(1,1-dimethylethoxy)carbonyl]-6-oxa-3-azabicyclo[3.1.0]hexane (1.32g, 7.13mmol) and benzylamine (2ml) in 1,4-dioxan (5ml) and water (5ml)

was heated at 85°C for 5h. The reaction was allowed to cool over 18h and the solid formed was collected by filtration and crystallised from ethyl acetate/cyclohexane to give the title compound (1.3g) nmr(δ,DMSO-d6) includes 1.4(s,9H), 2.32(bs,1H), 2.93(bs,1H), 3.1(bt,2H), 3.4(m,1H), 3.7(bs,2H), 3.97(bs,1h), 5.0(d,1H), 7.15-7.35(m,5H).

PREPARATION 22

[trans-(+/-)]-3-Amino-4-hydroxy-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester

A solution of [trans-(+/-)]-3-hydroxy-4-[(phenylmethyl)amino]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (1.1g, 3.76mmol) in ethanol (150ml) was hydrogenated over 10% palladium-on-carbon (0.05g) for 3.5h. The catalyst was removed by filtration, washed with ethanol (50ml) and the combined ethanolic solution was evaporated to leave an oil which was taken up in ethyl acetate (75ml). The solution was filtered and the filtrate evaporated to leave a solid which was crystallised from ethyl acetate/cyclohexane to give the title compound (0.643g), nmr(δ,$CDCl_3$) 1.45(s, 9H), 1.6-2.2(bm, 3H), 3.1(m,1H), 3.3(m,2H), 3.68(m,2H), 3.98(m,1H).

PREPARATION 23

1-Amino-cyclopropanemethanol

A slurry of lithium borohydride (0.771g,35.4mmol) in tetrahydrofuran (20ml) was stirred during the addition of chlorotrimethylsilane (9ml,70.8mmol) and the mixture was stirred for 5min on complete addition. 1-amino-1-cyclopropanecarboxylic acid (1.95g, 17.7mmol) was then added in portions over 5min and the mixture was stirred for 18h at room temperature. Methanol (30ml) was added dropwise over 10min then the mixture was concentrated to leave a gum which was treated with 20% potassium hydroxide solution(50ml) and extracted with dichloromethane (4x75ml). The combined extract was dried (Na_2SO_4) and evaporated to give the title compound (0.286g) as a solid, nmr(δ,$CDCl_3$) includes 0.5-0.6 and 0.6-0.7(m,4H), 1.8(s,3H), 3.47(s,2H).

PREPARATION 24

(+/-)-4-Trimethylsilyloxy-1H-pyrrolidin-2-one

(+/-)-4-Amino-3-hydroxybutyric acid (1.0g,8.39mmol), xylene (110ml), hexamethyldisilazane (12.4ml,58.7mmol) and chlorotrimethylsilane (2 drops) were heated at reflux for 4h then the cooled mixture was poured into ethanol (250ml).The resulting solution was evaporated to leave a solid which was taken up in chloroform (150ml) and filtered through celite. The filtrate was evaporated to dryness and the residue was purified by column chromatography on flash silica eluting with 5-25% methanol in chloroform to give the title compound (0.757g) as a solid, nmr(δ,$CDCl_3$) 0.1-0.2(m,9H), 2.28 and 2.55(dd and dd,2H), 3.25 and 3.6(dd and dd,2H), 4.5-4.6(m,1H), 5.6-5.7(m,1H).

PREPARATION 25

(+/-)-4-[(Methylsulphonyl)oxy]-1H-pyrrolidin-2-one

(+/-)-4-Trimethylsilyloxy-1H-pyrrolidin-2-one (2.0g,11.5mmol) in acetonitrile (30ml) was treated with 4M HCl (2.9ml,11.5mmol) and the mixture was stirred for 45min before evaporating to leave a brown oil. This oil was azeotroped with toluene (2x10ml) then taken up in acetone (40ml) and stirred with methanesulphonyl chloride (1.8ml,23mmol) and triethylamine (3.2ml,23mmol) for 2.5h. More methanesulphonyl chloride (0.9ml,11.5mmol) and triethylamine (1.6ml,11.5mmol) were added and the reaction was left for 16h. More methanesulphonyl chloride (1.35ml,17.3mmol) and triethylamine (2.4ml,17.3mmol) were added and the mixture was stirred for another 2h before evaporating to leave a solid which was purified by column chromatography on flash silica eluting with 5-10% methanol in chloroform to give the title compound (0.813g) as a solid which can be crystallised from ethyl acetate/cyclohexane, nmr(δ,$CDCl_3$) includes 2.59 and 2.78(dd and dd,2H), 3.09(s,3H), 3.68 and 3.81(bd and dd,2H), 5.37-5.45(m,1H), 5.5-5.7(m,1H).

PREPARATION 26

(+/-)-4-Amino-1H-pyrrolidin-2-one hydrochloride

A solution of (+/-)-4-[(methylsulphonyl)oxy]-1H-pyrrolidin-2-one (0.8g,4.9mmol) and sodium azide (0.348g,5.39mmol) in dimethylformamide (15ml) was stirred at room temperature for 65h then heated at 50°C for 6h. Water was added to the cooled reaction and the product was extracted into ethyl acetate (8x20ml) and the combined extract was dried (Na_2SO_4) and concentrated to 15ml. This solution was hydrogenated in ethanol (25ml) over 10% palladium-on-carbon

(0.165g) by bubbling hydrogen through the solution for 1h. The mixture was filtered through celite and the filtrate was concentrated to 10ml and this was stirred with 4M hydrochloric acid (0.88ml,4.9mmol). After 3h the mixture was evaporated and dried to give a solid which was stirred in ethanol for 0.5h and collected by filtration to give the title compound (0.402g,60%) nmr(δ, DMSO-d6)- includes 2.2-2.58(2xdd,2H), 3.24 and 3.55(2xdd,2H), 3.85-3.96(m,1H), 7.82-7.87(bs,1H), 8.3-8.5(bs,3H).

PREPARATION 27

[cis-(+/-)]-(2-Hydroxycyclopentyl)carbamic acid phenylmethyl ester

A solution of [cis-(+/-)]-2-aminocyclopentanol[1] (6.0g, 58.4mmol) in 1,4-dioxan (100ml) and water (50ml) was treated with sodium carbonate (30.9g, 292mmol) and benzyl chloroformate (8.34ml, 58.4mmol). The resulting mixture was stirred at 21°C overnight. It was then poured into 2N-hydrochloric acid (300ml) and extracted with ethyl acetate (3 x 100ml). The total organic solution was washed (brine,200ml), dried (Na_2SO_4) and evaporated to an oil (17.13g) which was purified on silica, eluting with cyclohexane: ethyl acetate (2:1) to give the title compound (6.089g) as a white solid, nmr(δ,$CDCl_3$) 1.4 to 2.1(m,7H), 3.88(m,1H), 4.18(m,1H), 5.11(br.s,3H), 7.35(m,5H).

1. R.A.B.Bannard et al., Canad.J.Chem.,1971,49,2064.

PREPARATION 28

[cis-(+/-)]-[2-[(Methylsulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester

Methanesulphonyl chloride (1.85ml, 23.9mmol) was added to a stirred mixture of [cis-(+/-)]-(2-hydroxycyclopentyl)carbamic acid phenylmethyl ester (2.50g, 10.6mmol) and triethylamine (3.35ml, 23.9mmol) in dichloromethane (125ml) at 21°C. The resulting yellow solution was stirred at 21°C overnight. It was then washed (water,100ml, then brine,100ml), dried (Na_2SO_4) and evaporated to a yellow oil (4.20g). The oil was purified on silica, eluting with cyclohexane:ethyl acetate (3:2) to give the title compound (3.29g) as a yellow oil which crystallised on standing, m.p. 74 to 76°C.

PREPARATION 29

[trans-(+/-)]-(2-Azidocyclopentyl)carbamic acid phenylmethyl ester

A solution of [cis-(+/-)]-[2-[(methylsulphonyl)oxy]cyclopentyl]carbamic acid phenylmethyl ester (3.23g, 10.3mmol) in N,N-dimethylformamide (50ml) and water (10ml) was stirred and treated with sodium azide (0.823g, 12.66mmol). The resulting solution was then stirred and heated in an oil-bath at 100°C for 2.5h, and was then left to cool to 21°C. The mixture was diluted with water (200ml) and extracted with ethyl acetate (3 x 100ml). The total organic solution was washed (water,2 x 100ml, then brine,200ml), dried (Na_2SO_4) and evaporated to a yellow oil (2.63g) which was purified on silica, eluting with cyclohexane: ethyl acetate (4:1) to give the title compound (2.00g) as a pale yellow oil, nmr (δ,$CDCl_3$) 1.4 to 1.55(m,1H), 1.6 to 1.8(m,3H), 1.9 to 2.05(m,1H), 2.05 to 2.2(m,1H), 3.72(m,1H), 3.90(m,1H), 4.70(br.s,1H), 5.12(s,2H), 7.35(m,5H); ir ($CHBr_3$) 2101cm^{-1} (N_3).

PREPARATION 30

[trans-(+/-)]-(2-Aminocyclopentyl)carbamic acid phenylmethyl ester

A solution of [trans-(+/-)]-(2-azidocyclopentyl)carbamic acid phenylmethyl ester (0.25g) in ethanol (20ml) was added slowly to a suspension of 10% palladium-on-carbon catalyst (0.025g) in ethanol (2ml) under nitrogen. Hydrogen was bubbled through the suspension for 20min and the mixture was then immediately purged with nitrogen and filtered through celite. The filtrate was evaporated to an oil (0.17g). The oil was dissolved in ethyl acetate (20ml) and extracted with 2N-hydrochloric acid (2 x 25ml). The total aqueous solution was covered with ethyl acetate (25ml) and basified with solid sodium carbonate. The aqueous layer was extracted with more ethyl acetate (25ml) and the total organic solution was washed (brine,30ml), dried (Na_2SO_4) and evaporated to give the title compound (0.104g) as a yellow oil, nmr (δ,$CDCl_3$) includes 1.3 to 1.5(m,2H), 1.55 to 1.85(m,2H), 1.9 to 2.25(m,2H), 3.03(q,1H), 3.60(m,1H), 4.75(br.s,1H), 5.10(s,2H), 7.35(m,5H).

PREPARATION 31

[(3aα,4α,6aα)-(+/-)]-N-[Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-N-(phenylmethyl)amine and

(1α,2β,3α)-2-(phenylmethyl)amino-1,3-cyclopentanediol

A mixture of [(1α,2β,5α)-(+/-)]-6-oxabicyclo[3.1.0]hexan-2-ol[1] (2.5g,25mmol), benzylamine (2.75ml,25.2mmol) and water (15ml) was stirred and heated at

reflux for 5h. The solution was evaporated to a brown oil which was dissolved in acetone (30ml) and treated with 2,2-dimethoxypropane (14ml) and 4-toluenesulphonic acid monohydrate (4.7g). The mixture was stirred and heated under reflux overnight and was then left to cool. The mixture was partitioned between 5% sodium hydrogen carbonate solution (200ml) and ethyl acetate (200ml). The aqueous layer was extracted with more ethyl acetate (2 x 100ml), and the aqueous and organic solutions were retained. The total organic solution was washed (brine,50ml), dried (Na_2SO_4) and evaporated to a brown oil which was purified on flash silica eluting with ethyl acetate:cyclohexane (3:1) to give [(3aα,4α,6aα)-(+/-)]-N-[tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-N-(phenylmethyl)amine (3.41g) as a pale brown oil, nmr(δ,$CDCl_3$) includes 1.30(s,3H), 1.42(s,3H), 1.5, 1.8, 2.0 (ms,4H), 3.80(br.s,2H), 4.24(d,1H), 4.74(t,1H), 7.2 to 7.45 (m,5H).

The combined aqueous layers were evaporated to a wet solid which was shaken with ethyl acetate (3 x 200ml). The organic solution was filtered, dried (Na_2SO_4) and evaporated to a white solid which was purified on flash silica eluting with dichloromethane:ethanol:0.880ammonia (50:8:1) to give (1α,2β,3α)-2-(phenylmethyl)amino-1,3-cyclopentanediol (0.410g) as an off-white solid nmr(δ,DMSO-d6) includes 1.4 to 1.6, 1.65 to 1.85(ms,4H), 2.05(br.s,1H), 2.61(t,1H), 3.6 to 3.75(m,2H), 3.81(s,2H), 4.67(d,2H), 7.15 to 7.4(m,5H).

1. T.Itoh et al., J.Am.Chem.Soc., 1979, 101, 159

PREPARATION 32

[(3aα,4α,6aα)-(+/-)]-Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amine

[(3aα,4α,6aα)-(+/-)]-N-[Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-N-(phenylmethyl)amine (3.2g,12.9mmol) in ethanol (80ml) was hydrogenated over 10% palladium-on-carbon catalyst (1.0g) for 5.5h. The catalyst was filtered off and the filtrate evaporated to give the title compound (2.02g) as a pale grey liquid, nmr(δ,DMSO-d6) 1.18(s,3H), 1.30(s,3H), 1.5 to 1.6, 1.65 to 2.0(ms,4H), 3.19(d,1H), 4.12(d,1H), 4.61(t,1H).

PREPARATION 33

(1α,2β,3α)-2-Amino-1,3-cyclopentanediol

(1α,2β,3α)-2-(Phenylmethyl)amino-1,3-cyclopentanediol (0.380g) in ethanol (20ml) was hydrogenated over 10% palladium-on-carbon catalyst (0.125g) for

7h. The catalyst was filtered off and the filtrate was evaporated to give the title compound (0.220g) as a pale-brown oil which solidified on storage at 4°C; nmr(δ,DMSO-d6) 1.45(m,2H), 1.75(m,2H), 3.2 to 3.55(m,3H), 4.7(m,2H).

PREPARATION 34

[1R-(exo,exo)]-5,6-Dihydroxy-2-azabicyclo[2.2.1]heptan-3-one

N-Methylmorpholine (12.67g,108mmol) in water (39ml) was stirred and treated with osmium tetroxide (2.5% solution in t-butanol) (4ml) and t-butanol (16ml). A slurry of [1R-(exo,exo)]-2-azabicyclo[2.2.1]hept-5-en-3-one[1] (10g,91.6mmol) in t-butanol (50ml) was added. The resulting brown-black solution was stirred at 70°C for 30 min and then as it cooled to 55°C over 25 min. Sodium hydrosulphite (0.900g) was added, and the mixture was cooled to 30°C and stirred at 30°C for 30 min. Activated charcoal (4g) was added and the mixture was stirred at 25 to 30°C for 30 min. The mixture was filtered through celite, and the residue washed with methanol (3 x 20ml). The total filtrate and washings were evaporated and azeotroped to dryness by evaporation from toluene (3 x 20ml). The residue in methanol (100ml) was heated to reflux, then filtered whilst hot and evaporated down to *ca* 35ml and left at 4°C overnight. The solid was filtered off, washed with cold methylated spirit (2 x 10ml) and dried to give the title compound (7.69g) as a brown solid, $[\alpha]_D$ -99° (H_2O, c=1.4%)

1. S.J.C.Taylor et al., J.Chem.Soc.,Chem.Commun., 1990, 1120.

PREPARATION 35

[1S-(1α,2β,3β,4α)]-4-Amino-2,3-dihydroxycyclopentanecarboxylic acid, methyl ester, hydrochloride salt

A solution of [1R-(exo,exo)]-5,6-dihydroxy-2-azabicyclo[2.2.1]heptan-3-one (11.815g) in 3N-hydrochloric acid (85ml) was stirred and heated at reflux for 1 h. The reaction mixture was evaporated in vacuo and was then evaporated from methanol (2 x 40ml) and then from toluene (6 x 40ml). The residue was treated with 1N methanolic HCl (70ml) and then heated at reflux for 2h. The cooled mixture was then concentrated by evaporation in vacuo and 2-propanol (100ml) was added and the mixture was stirred for 1h. The suspension was filtered and the residue dried to give the title compound (16.095g) as a grey solid, nmr(δ,DMSO-d6) 1.70(m,1H), 2.25(m,1H), 2.75(m,1H), 3.30(m,1H), 3.65(s,3H), 3.75(t,1H), 4.05(t,1H), 4.15(m,2H), 8.25(s,3H).

PREPARATION 36

[1S-(1α,2β,3β,4α)]-2,3-Dihydroxy-4-[[(phenylmethoxy)carbonyl]amino]-cyclopentanecarboxylic acid, methyl ester

A solution of [1S-(1α,2β,3β,4α)]-4-amino-2,3-dihydroxycyclopentanecarboxylic acid, methyl ester, hydrochloride salt (2.054g) in water (35ml) was cooled to 0°C and was treated with sodium carbonate (3.19g). The mixture was stirred for 10 min. then a solution of benzyl chloroformate (1.52ml) in 1,4-dioxan (60ml) was added dropwise. The reaction was stirred at 0° to 5°C for 30 min. then allowed to warm to 21°C and stirred for 2.5h. The suspension was diluted with ethyl acetate and washed with 2N-hydrochloric acid and the aqueous layer was extracted twice with fresh ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated to give the title compound (2.702g) as a white solid. A small amount (0.7g) was recrystallised from 2-propanol to give an analytical sample (0.058g) as white needles. Analysis found C,58.4, H,6.25, N,4.45%; $C_{15}H_{19}NO_6$ requires C,58.25, H,6.2, N,4.5%.

PREPARATION 37

[3aR-(3aα,4α,6α,6aα)]-Tetrahydro-2,2-dimethyl-6-[[(phenylmethoxy)carbonyl]amino]-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester

A solution of [1S-(1α,2β,3β,4α)]-2,3-dihydroxy-4-[[(phenylmethoxy)carbonyl]amino]-cyclopentanecarboxylic acid, methyl ester (21.385g) in acetone (400ml) was treated with 2,2-dimethoxypropane (75ml) and toluene-4-sulphonic acid (1.58g), and the solution was stirred at 21°C overnight. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and 8% sodium hydrogen carbonate solution. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated to a fawn solid which was recrystallised from di-isopropyl ether to give the title compound (18.452g) as white crystals, nmr(δ,$CDCl_3$) 1.30(s,3H), 1.45(s,3H), 1.95(d,1H), 2.45(m,1H), 3.00(d,1H), 3.70(s,3H), 4.15(t,1H), 4.50(d,1H), 4.80(d,1H), 5.10(t,2H), 5.70(m,1H), 7.35(m,5H).

PREPARATION 38

[3aR-(3aα,4α,6α,6aα)]-6-Amino-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester

A solution of [3aR-(3aα,4α,6α,6aα)]-tetrahydro-2,2-dimethyl-6-[[(phenylmethoxy)carbonyl]amino]-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester (18.4g,52.67mmol) in ethanol (400ml) was added to a suspension of 10% palladium-on-carbon catalyst (1.87g) in ethanol (100ml) under nitrogen. The mixture was then hydrogenated for 6.5h. The reaction mixture was filtered through celite and the filtrate evaporated to give the title compound (11.304g) as a pale yellow oil, nmr(δ,$CDCl_3$) 1.30(s,3H), 1.35(s,2H), 1.45(s,3H), 1.95(dt,1H), 2.30(dt,1H), 2.90(m,1H), 3.45(m,1H), 3.70(s,3H), 4.25(d,1H), 5.10(d,1H).

PREPARATION 39

[3aR-(3aα,4α,6α,6aα)]-Tetrahydro-6-(formylamino)-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester

Formic acetic anhydride (3.2g, 36.37mmol) was prepared from formic acid (1.37ml) and acetic anhydride (3.46ml) at 50°C for 2h. It was then added slowly in dry tetrahydrofuran (50ml) to a stirred solution of [3aR-(3aα,4α,6α,6aα)]-6-aminotetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester (6.062g, 28.16mmol) in ether (100ml). The mixture was stirred at 21°C for 2h and then evaporated to dryness. The residue was recrystallised from isopropyl ether to give the title compound (4.2434g) as pale pink crystals, nmr(δ,$CDCl_3$) 1.30(s,3H), 1.45(s,3H), 1.95(d,1H), 2.50(m,1H), 3.10(m,1H), 3.75(s,3H), 4.50(m,2H), 4.80(d,1H), 6.80(m,1H), 8.15(s,1H).

The mother liquors were evaporated and the residue was purified on silica eluting with dichloromethane:methanol 25:1 to give a further 1.762g of the title compound.

PREPARATION 40

[3aR-(3aα,4α,6aα)]-Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester

A solution of [3aR-(3aα,4α,6α,6aα)]-tetrahydro-6-(formylamino)-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester (6.014g, 24.72mmol) in dichloromethane (50ml) at -40°C was treated dropwise with triethylamine

(8.27ml, 59.33mmol) and phosphoryl chloride (2.31ml, 24.72mmol). The reaction was stirred at -40°C for 20min., then allowed to warm to 21°C and stirred for 5h. The mixture was poured into ice/water (300ml) containing sodium carbonate (25g) and extracted with dichloromethane (2 x 100ml). The combined organic phases were washed with brine (200ml), dried (Na_2SO_4) and evaporated and azeotroped with toluene (2 x 50ml). The residue was stored at 4°C overnight. A solution of tri-n-butyltin hydride (9.31ml, 34.61mmol) in dry toluene (400ml) was heated at 100°C under nitrogen and treated dropwise over 20min. with a solution of the above residue in dry toluene (150ml). 2,2'-Azobis-(2-methylpropionitrile) (0.27g) was added at the same time. The reaction was stirred at 110°C for 2h, then allowed to cool to 21°C and evaporated in vacuo. The residue was purified on silica eluting with cyclohexane:ethyl acetate (2:1) to give the title compound (2.709g) as a clear oil, nmr(δ,$CDCl_3$) 1.30(s,3H), 1.45(s,3H), 1.70 to 1.95(m,3H), 2.10(m,1H), 2.90(d,1H), 3.70(s3H), 4.70(t,1H), 4.85(d,1H).

PREPARATION 41

[3aR-(3aα,4α,6aα)]-Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid

[3aR-(3aα,4α,6aα)]-Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid, methyl ester (2.492g, 12.45mmol) in water (50ml) and methanol (5ml) was treated with potassium hydroxide (2.10g 37.35mmol), and the mixture was stirred briskly at 21°C for 2.5h. The reaction mixture was then washed with ethyl acetate (50ml), then cooled in ice and covered with ethyl acetate (50ml). The mixture was acidified to pH 2 with 2N-hydrochloric acid and the aqueous layer was extracted with more ethyl acetate (2 x 25ml). The combined organic layers were washed with brine (50ml), dried (Na_2SO_4) and evaporated to give the title compound (2.318g) as white crystals. A small amount was recrystallised from hexane to give an analytical sample (0.13g), m.p.72 to 73°C. Analysis found C,58.1, H,7.7%; $C_9H_{14}O_4$ requires C,58.05, H,7.6%.

PREPARATION 42

[3aR-(3aα,4α,6aα)]-(Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl)carbamic acid, phenylmethyl ester

A solution of [3aR-(3aα,4α,6aα)]-t trahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-carboxylic acid (4.27g,22.9mmol) in dry 1,4-dioxan (100ml) under nitrogen was treated with benzyl alcohol (4.75ml,45.88mmol), triethylamine (3.20ml,22.94mmol) and diphenylphosphoryl azide (4.94ml,22.94mmol). The resulting solution was stirred and heated at 90°C overnight, then allowed to cool to 21°C, concentrated in vacuo and the residue dissolved in ethyl acetate (100ml) and washed with 1N-hydrochloric acid. The aqueous layer was extracted with ethyl acetate (100ml) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to an oil. In order to remove excess benzyl alcohol as benzyl acetate, the oil was dissolved in dichloromethane (150ml), cooled to 5 to 10°C and treated with 4-dimethylaminopyridine (5.6g,45.9mmol) and acetic anhydride (4.33ml,45.9mmol). The resulting solution was stirred at 21°C for 1.5h, then washed with 2N-hydrochloric acid (100ml). The aqueous layer was extracted with dichloromethane (2 x 100ml) and the combined organic extracts were washed (brine,200ml), dried (Na_2SO_4) and evaporated to an oil which was purified on silica eluting with ether:cyclohexane 2:1 to give the title compound (4.588g) as a white solid, nmr(δ,$CDCl_3$) 1.30(s,3H), 1.45(s,3H), 1.55(m,1H), 1.75(m,1H), 1.90(dd,1H), 2.10(m,1H), 3.95(t,1H), 4.45(d,1H), 4.60(m,1H), 4.70(t,1H), 5.10(s,2H), 7.35(s,5H).

PREPARATION 43

[3aR-(3aα,4α,6aα)]-Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amine

A solution of [3aR-(3aα,4α,6aα)]-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl)carbamic acid, phenylmethyl ester (2.0g, 6.86mmol) in ethanol (80ml) was added dropwise to a stirred suspension of 10%-palladium-on-carbon catalyst (0.20g) in ethanol under nitrogen. The suspension was hydrogenated at 21°C for 4.5h, then filtered through celite. The filtrate was evaporated to give the title compound (1.053g) as a clear oil, nmr(δ,$CDCl_3$) 1.25 to 1.45(m,9H), 1.75 to 2.10(m,3H), 3.40(d,1H), 4.20(d,1H), 4.75(t,1H).

PREPARATION 44

(S)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexanedioic acid 1-methyl 6-(phenylmethyl) ester

4-Methylmorpholine (2ml) was added to a solution of t-butoxycarbonyl-L-glutamic acid 5-benzyl ester (6.75g,20mmol) in ethyl acetate (60ml) at 0°C. i-Butyl chloroformate (2.61ml,20mmol) was then added to give a precipitate and the mixture was stirred for 15min at 0°C before filtering through celite into a flask at 0°C. The pad was washed with precooled ethyl acetate. The combined filtrate and wash was treated with diazomethane in ether (30mmol in 100ml) over 5min and the reaction left at 0°C for 3h before warming to room temperature. Excess diazomethane was removed by bubbling nitrogen through the solution which was then concentrated to give a yellow gum. The gum was dissolved in methanol (100ml), treated with silver benzoate (1g, 4.4mmol) and triethylamine (10ml,70mmol) then stirred for 2.5h at room temperature. The black solution was concentrated under reduced pressure and the residue taken up in ethyl acetate (100ml) then washed with saturated aqueous sodium bicarbonate solution (100ml), water (100ml), 1M aqueous potassium hydrogen sulphate solution (2x100ml) and brine (100ml). The dried ($MgSO_4$) organic phase was evaporated to leave a yellow oil which was purified by column chromatography on flash silica eluting with a gradient of 15-50% ethyl acetate in cyclohexane to give the title compound (1.972g) as a white solid which crystallised from cyclohexane m.p.60-61°C, $[\alpha]_D$ -21° ($CHCl_3$ c=1%).

PREPARATION 45

(S)-(3-Oxocyclopentyl)carbamic acid 1,1-dimethylethyl ester

2.5M n-Butyllithium in hexane (5.83ml) was added dropwise to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (3.16ml,15mmol) in tetrahydrofuran (30ml) at 4°C. After 20min the solution was cooled to -60°C and (S)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-hexanedioic acid 1-methyl 6-(phenylmethyl) ester (1.522g,4.16mmol) in tetrahydrofuran (10ml) was added dropwise over 5min. The solution was stirred for 10min before the addition of pH7 buffer (5ml) and the mixture was then diluted with dichloromethane (200ml) and pH7 buffer (300ml). The aqueous phase was adjusted to pH6.5 with 2M hydrochloric acid and then the organic phase was separated. The aqueous phase was extracted with dichloromethane (2x200ml) and the combined organic phase was dried ($MgSO_4$) then evaporated to leave a solid.The solid was dissolved in ethanol (45ml) and hydrogenated over 10% palladium-on-carbon (0.5g) for 4h. The hydrogen was replaced by nitrogen and the reaction was stirred for a further

18h then filtered through celit and the pad was washed with ethanol. The filtrate and washings were combined and evaporated to leave a solid which was purified by column chromatography on flash silica eluting with 25-40% ethyl acetate in cyclohexane to give the title compound (0.437g) as a white solid which crystallised from isopropyl ether, m.p. 97-98°C, $[\alpha]_D$ -48° ($CHCl_3$ c=0.52%).

PREPARATION 46

(1S-trans)-(3-Hydroxycyclopentyl)carbamic acid 1,1-dimethylethyl ester

A 1M solution of lithium tris(1,2-dimethylpropyl)borohydride in tetrahydrofuran (1.99ml) was diluted with tetrahydrofuran (3ml), cooled to -78°C and treated dropwise with a solution of (S)-(3- oxocyclopentyl)carbamic acid 1,1-dimethylethyl ester (0.38g,1.66mmol) in dry tetrahydrofuran (2ml) at 0°C. The reaction was stirred for 2h at -78°C then allowed to warm to room temperature over 1h. Water (2ml) was added dropwise then the mixture was diluted with water (20ml) and ethyl acetate (30ml). The organic phase was washed with water (20ml), dried ($MgSO_4$) and evaporated to give impure product which was purified by chromatography on flash silica eluting initially with 15% ethyl acetate in cyclohexane and progressing to neat ethyl acetate. Early fractions gave (1S-cis)-(3-hydroxycyclopentyl)carbamic acid 1,1-dimethylethyl ester (0.16g) as an oil, nmr (d,$CDCl_3$) 1.43(s,9H), 1.50-2.10(m,6H), 3.97-4.10(m,1H), 4.32-4.40(m,1-H), 5.00-5.12(m,1H).

Later fractions gave the title compound (0.124g) as a solid which was crystallised from diisopropyl ether m.p. 83-85°C, $[\alpha]_D$ +1.4° ($CHCl_3$ c=0.54%).

PREPARATION 47

(1S-trans)-[3-(Formyloxy)cyclopentyl]carbamic acid 1,1-dimethylethyl ester

Diethyl azodicarboxylate (0.164ml, 1.23mmol) was added dropwise to a stirred solution of (1S-cis)-(3-hydroxycyclopentyl)carbamic acid 1,1-dimethylethyl ester (0.124g, 0.61mmol), triphenylphosphine (0.323g, 1.23mmol) and formic acid (0.046ml, 1.23mmol) and the solution was stirred at room temperature for 2h. The solution was then concentrated and purified by column chromatography on flash silica eluting with 10-30% ethyl acetate in cyclohexane to give the title compound (0.07g) as white needles from diisopropyl ether m.p.84-85°C, $[\alpha]_D$ -12.7° ($CHCl_3$ c=0.55%).

PREPARATION 48

(1S-trans)-(3-Hydroxycyclopentyl)carbamic acid 1,1-dimethylethyl ester

A solution of (1S-trans)-[3-(formyloxy)cyclopentyl]carbamic acid 1,1-dimethylethyl ester (0.081g, 0.35mmol) in methanol (3ml) was treated with a slurry of potassium hydrogen carbonate (0.707g, 7.06mmol) in water (1.5ml) and stirred at room temperature for 2h. The mixture was then diluted with water (20ml) and ethyl acetate (20ml) and the aqueous phase was extracted with ethyl acetate (2x20ml). The combined organic phase was dried ($MgSO_4$) and evaporated to leave a solid which was purified by column chromatography on flash silica eluting with 30-40% ethyl acetate in cyclohexane to give the title compound (0.037g) from diisopropyl ether m.p. 83-85°C, $[\alpha]_D$ 0.0° ($CHCl_3$ c=0.55%).

PREPARATION 49

(S)-[1-[[(Methylsulphonyl)oxy]methyl]-2-phenylethyl]carbamic acid phenylmethyl ester

Methanesulphonyl chloride (6.45ml) was added to a stirred solution of (S)-[1-(hydroxymethyl)-2-phenylethyl]carbamic acid phenylmethyl ester[1] (12.0g,0.042mole) and triethylamine (11.7ml) in acetone (190ml). On complete addition the mixture was stirred for 0.5h then diluted with water (700ml) and ethyl acetate (600ml). The aqueous phase was extracted with ethyl acetate (2x500ml) and the combined organic solution was washed with water (2x500ml), dried ($MgSO_4$) and evaporated to leave a solid which was purified by flash chromatography using 40-60% ethyl acetate in cyclohexane to give the title compound (13.95g), MH^+=364.

1. A.Correa et al., Synth.Commun., 1991, 21(1), 1.

PREPARATION 50

(S)-[1-(Azidomethyl)-2-phenylethyl]carbamic acid phenylmethyl ester

A solution of (S)-[1-[[(methylsulphonyl)oxy]methyl]-2-phenylethyl]carbamic acid phenylmethyl ester (2.0g,5.5mmol) in dimethylformamide (35ml) was heated with sodium azide (0.43g,6.6mmol) at 80°C for 4.5h. The reaction was then cooled and poured into iced water (100ml) and ethyl acetate (70ml). The aqueous phase was extracted with ethyl acetate (2x70ml) and the combined

xtract was washed with water (50ml), dried ($MgSO_4$) and evaporated to l ave an oil which was purified by flash chromatography eluting with 20% ethyl acetate in cyclohexane to give the title compound (1.51g) as an oil, MH^+=312.

PREPARATION 51

(S)-[1-(Aminomethyl)-2-phenylethyl]carbamic acid phenylmethyl ester

A solution of (S)-[1-[(azidomethyl)-2-phenylethyl]carbamic acid phenylmethyl ester (0.104g,0.323mmol) in ethanol (5ml) was hydrogenated over 10% palladium-on-carbon (0.019g) by bubbling hydrogen through for 20min. The catalyst was removed by filtration and the filtrate was evaporated to leave an oil which was taken up in ethyl acetate (15ml) and the solution was filtered. The filtrate was evaporated to give the title compound (0.102g) as an oil which solidified on standing, MH^+=284.

PREPARATION 52

(S)-[1-[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]-2-phenylethyl]carbamic acid phenylmethyl ester

Water (80ml), sodium carbonate (3.91g,3.69mmol) and di-t-butyl pyrocarbonate (8.05g,3.69mmol) were added to a solution of (S)-[1-(aminomethyl)-2-phenylethyl]carbamic acid phenylmethyl ester (3.5g, 12.3mmol) in 1,4-dioxan (80ml) and the mixture was stirred for 3.3h. Ethyl acetate (500ml) and water (500ml) were added and the aqueous phase was extracted with ethyl acetate (2x500ml). The combined organic phase was dried ($MgSO_4$) and evaporated to leave a solid which was purified by column chromatography on flash silica eluting with 10-27% ethyl acetate in cyclohexane to give the title compound (3.093g) as a solid, nmr(δ,$CDCl_3$) includes 1.42(s,9H), 2.76 and 2.82-2.93(dd and m,2H), 3.1-3.3(m,2H), 3.87-4.0(m,1H), 5.08(s,2H), 7.1-7.4(m,10H).

PREPARATION 53

(S)-(2-Amino-3-phenylpropyl)carbamic acid 1,1-dimethylethyl ester

A mixture of (S)-[1-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]-2-phenylethyl]carbamic acid phenylmethyl ester (2.89g,7.51mmol) and 10% Pd-C (0.171g) in ethanol (70ml) was stirred under hydrogen for 2 days. The reaction mixture was filtered through celite and the filtrate was evaporated to leave the title compound (2.18g) as a solid, nmr(δ,$CDCl_3$) includes 1.43(s,9H), 2.5-2.62

and 2.83(m and dd,2H), 3.0 and 3.1-3.25(m,2H), 3.25-3.4(m,1H), 5.0-5.15(m,1H), 7.15-7.35(m,5H).

PREPARATION 54

(S)-[1-(Hydroxymethyl)-2-(3-pyridinyl)ethyl]carbamic acid 1,1-dimethylethyl ester

A mixture of (S)-[2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-(3-pyridinyl)]propionic acid (1.804g,6.77mmol) in dry tetrahydrofuran (30ml) was cooled to -10°C and treated dropwise with 4-methylmorpholine (0.74ml,6.77mmol) and after 5min with ethyl chloroformate (0.65ml,6.77mmol). The solution was stirred for 25 min then added in portions after filtration to a stirred solution of sodium borohydride (0.64g,16.1mmol) in water (25ml) at 0°C. The reaction was stirred for 25min then allowed to warm to room temperature over 3h. The pH of the solution was adjusted to pH3 with 2M hydrochloric acid and stirred for 0.7h before bringing the pH to 7 with sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate (3x150ml) and the extract was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (100:8:1). Impure fractions from this column were repurified and added to the pure fractions from the column to give the title compound (1.274g) as a solid, nmr(δ, $CDCl_3$) includes 1.4(s,9H), 2.8-2.95(m,2H), 3.61(m,2H), 3.8-3.9(m,1H), 4.8-4.9(m,1H), 7.2-7.3,7.6 and 8.45-8.52(m,d,m,4H).

PREPARATION 55

(S)-β-Amino-3-pyridinepropanol dihydrochloride

To a solution of (S)-[1-(hydroxymethyl)-2-(3-pyridinyl)ethyl]carbamic acid 1,1-dimethylethyl ester (1.27g,5.03mmol) in 1,4-dioxan (3ml) was added 1,4-dioxan saturated with HCl gas (10ml) followed by a further portion of 1,4-dioxan (10ml). After 2h at room temperature the precipitated solid was collected by filtration, washed with 1,4-dioxan (5ml) and ether then dried in vacuo to give the title compound (0.928g) as a solid, nmr(δ,DMSO-d6) includes 3.11(bd,2H), 3.4-3.7(m,3H), 7.86(dd,1H), 8.1-8.3(bs,3H), 8.45(d,1H), 8.81(d,1H), 8.9(s,1H).

PREPARATION 56

(3aα,5α,6aα)-(T trahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-5-yl)carbamic acid, phenylmethyl ester

A solution of (3aα,5α,6aα)-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-5-carboxylic acid[1] (2.00g,10.74mmol) in dry 1,4-dioxan under nitrogen was treated with benzyl alcohol (2.22ml, 21.5mmol), triethylamine (1.50ml, 10.74mmol) and diphenylphosphoryl azide (2.31ml, 10.74mmol). The resulting solution was stirred in an oil-bath at 90°C overnight and was then allowed to cool to 21°C. The mixture was evaporated, and the residue was partitioned between ethyl acetate (80ml) and 1N hydrochloric acid (80ml). The aqueous layer was extracted with fresh ethyl acetate (50ml) and the total organic solution was washed (brine, 100ml), dried (Na_2SO_4) and evaporated to a pale yellow oil (7.24g). The oil was purified on silica, eluting with diethyl ether:cyclohexane (2:1) to give the title compound (2.055g) as a white solid, nmr(δ,$CDCl_3$) 1.25(s,3H), 1.3 to 1.5(m,2H), 1.45(s,3H), 2.25(dd,2H), 4.25(m,1H), 4.5 to 4.7(m,3H), 5.10(s,2H), 7.3 to 7.4(m,5H).

[1] W.H.Rastetter and D.P.Phillion, J.Org.Chem., 1981, 46, 3204

PREPARATION 57

(3aα,5α,6aα)-Tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-5-amine

A solution of (3aα,5α,6aα)-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-5-yl)carbamic acid, phenylmethyl ester (2.05g,7.06mmol) in ethanol (50ml) was added dropwise to a stirred suspension of 10% palladium-on-carbon (0.210g) in ethanol under nitrogen. The mixture was then stirred and hydrogenated overnight. The mixture was filtered through celite and the filtrate was evaporated to give the title compound (1.24g) as a pale yellow oil which solidified on standing at 4°C, m.p. 55 to 57°C, nmr(δ,$CDCl_3$) includes 1.25(s,3H), 1.2 to 1.5(m,2H), 1.45(s,3H), 2.10(dd,2H), 3.60(m,1H), 4.52(m,2H).

PREPARATION 58

(1α,2α,4β)-4-Amino-1,2-cyclopentanediol, hydrochloride

A solution of (3aα,5α,6aα)-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-5-yl)carbamic acid, phenylmethyl ester (Preparation 56) in ethanol (70ml) was added dropwise to 10% palladium-on-carbon (0.190g) under dry nitrogen. The mixture was hydrogenated at 21°C overnight and then filtered through celite. The filtrate was treated with 2.5M hydrogen chloride in ethanol (20ml) and

water (2ml),and the mixtur was h ated at 65°C for 3.5h. The mixture was evaporated and the residue was treated with more 2.5M hydrogen chloride in ethanol (15ml) and water (1ml). The solution was heated at 65°C for 2h, then it was evaporated to a white solid (0.995g). The solid was recrystallised from methanol/ethyl acetate to give the title compound (0.373g) as white crystals, nmr(δ,DMSO-d6) 1.6 to 1.8(m,2H), 1.8 to 2.0(m,2H), 3.60(m,1H), 4.00(s,2H), 4.60(br.s,1H), 8.05(br.s,3H).

PREPARATION 59

5-Amino-1H-tetrazoleethanamine

A mixture of 5-aminotetrazole (6.0g, 58.2mmol) and solid sodium hydroxide (8.36g, 208mmol) in acetonitrile (30ml) was stirred for 0.5h. 2-Chloroethylamine hydrochloride (7.26g, 62.4mmol) and tetrabutylammonium hydrogen sulphate (0.788g, 2.32mmol) were added and the reaction was heated at reflux for 18h. The mixture was filtered and the filtrate was evaporated to leave an oil which was taken up in 48% aqueous HBr. The solution was diluted with ethanol (150ml) and then evaporated to leave an oil which soon solidified. The solid was leached with hot ethanol leaving a brown gum which was dissolved in water and the solution was evaporated to dryness to give a solid (1.62g) after drying. The ethanol was reduced in volume and allowed to crystallise. The resulting solid (0.879g) and the solid from the aqueous solution were combined and stirred in ethanol with a slight excess of sodium hydroxide until a clear solution was obtained. This solution was preabsorbed onto flash silica and purified by elution with dichloromethane:ethanol:0.88 ammonia (100:8:1) to (30:8:1). Fractions with product were evaporated to leave the title compound (0.217g) as an oil. MH^+=129.

PREPARATION 60

(trans)-(4-Aminocyclohexyl)carbamic acid phenylmethyl ester

A solution of trans 1,4-cyclohexanediamine (22.8g, 200mmol) in dry dioxan (100ml) was cooled to 5-10° and treated dropwise with 1-[[(phenylmethoxy)carbonyl]oxy]-2,5-pyrrolidinedione (4.98g, 20mmol) in dioxan (50ml) over 3h. The mixture was warmed to 21° then stirred for a further 2h and filtered. The filtrate was evaporated to give a solid which was purified on silica

eluted with dichloromethane:ethanol:0.88 ammonia (30:8:1) to give the title compound (2.58g) as a white solid. MH^+=249.

PREPARATION 61

trans-(4-N,N-Dimethylaminocyclohexyl)carbamic acid phenylmethyl ester

A solution of (trans)-(4-amino-cyclohexyl)carbamic acid phenylmethyl ester (0.2g, 0.805mmol) in formaldehyde (5ml) and formic acid (0.1ml) was heated at reflux for 1.5h. More formaldehyde (2.5ml) was added and the reaction continued for a further 2.5h. The cooled mixture was poured into saturated sodium bicarbonate solution (50ml) and extracted with ethyl acetate (3x30ml). The combined organic extract was washed with water (2x30ml), dried (MgSO4) and evaporated to give an oil which was purified on silica eluted with dichloromethane:ethanol:0.88 ammonia (30:8:1) to give the title compound as an oil. MH^+=279.

PREPARATION 62

trans-(4-N,N-Dimethylamino)cyclohexylamine

A solution of trans-(4-N,N-dimethylaminocyclohexyl)carbamic acid phenylmethyl ester (0.245g, 0.887mmol) in ethanol (10ml) was hydrogenated over 10% palladium-on-carbon (0.03g) for 50h with two further changes of catalyst (0.05g each). The reaction mixture was filtered and the catalyst was washed with ethanol. Evaporation of the filtrate and wash gave the title compound (0.097g) as an oil, nmr(δ,$CDCl_3$) includes 1.0-1.05(m,2H), 1.1-1.4(m,2H), 1.4-1.8(m,2H), 1.8-2.05(m,4H), 2.05-2.25(m,1H), 2.27(s,6H), 2.58-2.72(m,1H).

PREPARATION 63

(1S-cis)-[3-[(Methylsulphonyl)oxy]cyclopentyl]carbamic acid 1,1-dimethylethyl ester

Methanesulphonyl chloride (0.98ml, 12.6 mmol) was added to a stirred mixture of (1S-cis)-(3-hydroxycyclopentyl)carbamic acid 1,1-dimethylethyl ester (1.41g, 7.01mmol) and triethylamine (1.76ml, 12.6mmol) in acetone(55ml) at 4°C. The resulting mixture, containing a white precipitate, was stirred at 4°C for one hour, then at 21°C for a further 2.25h, after which it was diluted with water(150ml) and extracted with ethyl acetate (3 x 100ml). The total organic solution was washed with water (50ml), dried ($MgSO_4$) and evaporated to a white solid. This was

dissolved in hot diethyl ther(25ml) and cooled to 4°C for 2h, after which time, cyclohexane(25ml) was added which caused a precipitate to form immediately. The mixture was left to stand at 4°C for a further 3h, after which the solid was filtered off, washed with cold cyclohexane/diethyl ether(2:1), then dried to give the title compound (1.202g) as a white solid, m.p. 88-89°C, $[\alpha]_D$ -11.11° ($CHCl_3$ c=0.54%).

PREPARATION 64

(1S-trans)-[3-(N,N-Dimethylamino)cyclopentyl]carbamic acid 1,1-dimethylethyl ester

(1S-cis)-[3-[(Methylsulphonyl)oxy]cyclopentyl]carbamic acid 1,1-dimethylethyl ester (1.452g, 5.20mmol) in a solution of dimethylamine (33% in ethanol, 25ml) was heated at reflux for 3.75h, then allowed to cool. The solution was diluted with water(100ml) and extracted with ethyl acetate(3 x 100ml). The total organic solution was dried (Na_2SO_4) and evaporated to a yellow gum. This was purified on silica, eluting with dichloromethane:ethanol:0.88 ammonia (100:8:1) changing to (30:8:1) to give a brown film (0.988g, 83%). A portion of this was evaporated from a solution in isopropyl ether to give the title compound (0.139g) as a brown solid, m.p. 65-67°C, $[\alpha]_D$-40.35° ($CHCl_3$ c=0.57%).

PREPARATION 65

(1S-trans)-3-(N,N-Dimethylamino)cyclopentylamine dihydrochloride salt.

(1S-trans)-[3-(N,N-Dimethylamino)cyclopentyl]carbamic acid 1,1-dimethylethyl ester (0.537g, 2.35mmol) in 1,4-dioxan (4ml) was treated with a saturated solution of hydrogen chloride in 1,4-dioxan (15ml) and additional 1,4-dioxan (8ml). After 50 minutes at 21°C, another portion of a saturated solution of hydrogen chloride in 1,4-dioxan (5ml) was added, and after a further 2.5h, the opaque solution was concentrated by evaporation to give the title compound as a beige solid, which was used without characterisation.

PREPARATION 66

6-Amino-2-pyridinemethanamine

A solution of 6-acetylaminopyridine-2-carboxaldehyde[1] (0.65g, 3.96mmole) in ethanol (150ml) was saturated with ammonia and hydrogenated over 10% Pd-C (0.32g) for 24h. The catalyst was removed by filtration through kieselguhr and

the catalyst was washed with ethanol (2x50ml). The filtrate and wash were evaporated to leave a solid which was taken up in 2M sodium hydroxide solution (20ml) and heated at 60° for 2h. The cooled mixture was evaporated to low bulk (~1.5ml) and extracted with dichloromethane (5x20ml). The extract was dried ($MgSO_4$) and evaporated to leave the crude title compound as an oil which was used without further purification.

1. Abarca, B.,et al., Tetrahedron, 1989, 45(22), 7041.

EXAMPLE 1

(1S-trans)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

(1S-trans)-N-(3-Hydroxycyclopentyl)carbamic acid 1,1-dimethylethyl ester (0.138g, 0.69mmol) in 1,4-dioxan (2ml) was treated with a saturated solution of hydrogen chloride in 1,4-dioxan (2ml) for 0.5h. The solution was evaporated to dryness, azeotroped with methanol (2x5ml), then dissolved in methanol (4ml) and added to a solution of sodium hydroxide (0.011g, 0.65mmol) in methanol (4ml). The methanol was blown off with nitrogen and the resulting film was dissolved in dimethylsulphoxide (0.5ml). This solution was added to 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.127g, 0.69mmol) and the mixture was heated at 140°C for 27h. The cooled mixture was diluted with ethyl acetate (40ml) and water (40ml) and the organic phase was washed with water (30ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluting initially with 60% ethyl acetate in cyclohexane and progressing to neat ethyl acetate to give the title compound (0.029g) which crystallised from ethyl acetate/cyclohexane MH^+=628, $[\alpha]_D$+1.9°($CHCl_3$ c=0.53%).

EXAMPLE 2

(1S-trans)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide hydrochloride salt

A solution of (1S-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-

D-ribofuranuronamide (0.01g, 0.02mmol) in 1,4-dioxan(1.5ml) was tr at d with 6M-aqueous hydrochloric acid (3ml) and the solution was left to stand for 4 days before evaporating to leave the title compound (0.029g) as a glassy solid, MH^+=588, nmr(δ,$CDCl_3$) includes 1.02(t,3H),1.4-1.6, 1.6-1.8, 1.85-2.05, 2.1-2.25(ms,6H), 3.1-3.2(m,2H), 4.35(s,1H), 5.85-5.9(m,1H), 7.1-7.4(m,10H).

EXAMPLE 3

[trans-(+/-)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.7g, 1.24mmol) and trans-(+/-)-3-aminocyclopentanol[1] (0.844g, 7.23mmol) in dimethylsulphoxide (3ml) was heated at 140°C for 24h. The solution was diluted with ethyl acetate (90ml), washed with water (3x100ml) then dried ($MgSO_4$) and evaporated to leave a froth which was purified by column chromatography on flash silica initially eluting with 65% ethyl acetate in cyclohexane and progressing to neat ethyl acetate to give the title compound (0.498g) as a froth MH^+=628, nmr(δ,$CDCl_3$) includes 0.705-0.715(ts,3H), 1.4(s,3H) and 1.59(s,3H), 1.55-2.3(ms,6H), 2.9-3.05(m,2H), 4.15-4.55(ms,5H), 4.65(bd, 1H), 5.5-5.6(m,1H), 5.6-5.7(m,1H), 5.99(d,1H), 7.2-7.4(m,10H), 7.41(s,1H).

1. Published European Application EP-A-322242.

EXAMPLE 4

[trans-(+/-)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of [trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.137g,0.218mmol) in 95:5 trifluoroacetic acid:water (5ml) was kept at room temperature for 4h then the solvent was removed by evaporation. The residue was purified by preparative HPLC (30-70% acetonitrile) to give the title compound (0.033g), nmr(δ,DMSO-d6) includes 1.0(t,3H), 1.5(m,2H), 1.6-1.8(m,1H), 1.8(m,2H), 2.0-2.3(m,1H), 3.15(m,2H), 4.0-4.4(m,6H), 4.4-4.7(m,3H), 5.85(d,1H), 7.1-7.4(m,10H), 8.1-8.4(m,2H).

EXAMPLE 5

(1R-trans)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide and (1S-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of [trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.433g, 0.69mmol) in 1,4-dioxan (9ml) was stirred with 2M hydrochloric acid (11ml) for 25h. More acid (4M,2ml) was added and the mixture was kept at 3° for 65h before evaporating to leave a solid which was purified by preparative HPLC (39% acetonitrile for 16min then up to 42% over 5min and up to 45% over 1min) to give the (1R) isomer (0.142g) as a solid from ether MH^+=588, nmr(d,$_1$DMSO-d6) includes 1.01(t,3H), 1.4-1.6, 1.6-1.8, 1.8-2.0, 2.1-2.25(ms,6H), 3.1-3.25(m,2H), 4.3(s,1H), 5.85(bd,1H), 7.1-7.4(m,10H), 8.15(bs,1H), then the (1S) isomer (0.14g) as a solid from ether MH^+=588, nmr(δ,DMSO-d6) includes 1.01(t,3H), 1.4-1.6, 1.6-1.8, 1.8-2.0, 2.1-2.25(ms,6H),3.1-3.25(m,2H), 4.3(s,1H), 5.84(bd,1H), 7.15-7.4(m,10H), 8.03(bs,1H).

EXAMPLE 6

[3aR-(3aα,4α,6aα)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amino)-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.346g, 0.614mmol) and [3aR-(3aα,4α,6aα)]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amine (0.965g, 6.14mmol) was dissolved in dimethylsulphoxide (1.8ml), and the solution was stirred and heated at 140°C under nitrogen for 11h. The mixture was allowed to cool to 21°C and was then partitioned between ethyl acetate (50ml) and water (50ml). The organic layer was washed with water and the combined aqueous layers were extracted with ethyl acetate (2 x 30ml). The combined organic extracts were washed (brine), dried (Na_2SO_4) and evaporated. The residue was purified on silica eluting with ethyl acetate:cyclohexane (9:1), and then repurified on silica eluting with ethyl

acetate:cyclohexane (3:1) to give the title compound (0.302g) as a cream foam, MH^+= 684.

Similarly prepared was:

[(3aα,4α,6aα)-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amino)-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide from the 2-chloropurine (0.269g) and [(3aα,4α,6aα)-(+/-)]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amine (0.75g) in dimethylsulphoxide (1.5ml) at 140°C for 20h. The product was purified on silica eluting with ethyl acetate:cyclohexane 9:1, MH^+= 684.

EXAMPLE 7

[1S-(1α,2β,3β)]-1-Deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

[3aR-(3aα,4α,6aα)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amino)-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.13g, 0.19mmol) was treated with trifluoroacetic acid (1ml) and water (0.25ml), and the resulting solution was left to stand at 21°C for 1.5h. The reaction mixture was evaporated, and the residue was purified on silica eluting with dichloromethane:methanol (9:1) to give the title compound (0.080g) as a cream foam; MH^+=604. (δ,DMSO-d6) 1.00(t,3H), 1.35(m,1H), 1.55(m,1H), 1.85(m,1H), 2.20(m,1H), 3.15(m,1H),3.75(m,1H), 3.90 to 4.25(m,6H), 4.40(m,1H), 4.65(m,2H), 5.50(d,1H), 5.60(d,1H), 5.80(d,1H), 6.35(m,1H), 7.10 to 7.45(m,11H), 7.95(s,1H), 8.15(m,1H).

EXAMPLE 8

[(1α,2β,3β)-(+/-)]-1-Deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide,

[1R-(1α,2β,3β)]-1-deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, and

[1S-(1α,2β,3β)]-1-deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

[(3aα,4α,6aα)-(+/-)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-(tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-amino)-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.222g) was treated with trifluoroacetic acid (2.5ml) and water (0.25ml), and the resulting solution was left

to stand at 20°C for 3h. The reaction mixture was evaporated, and the residue was stirred with sodium hydrogen carbonate (2.4g) in ethanol (6ml) at 20°C for 1h. The total filtrate and washings were evaporated and the residue was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (30:8:1) to give the first title compound (0.089g) as a pale brown solid, MH^+= 604, Analysis found: C,59.05, H,6.1, N,15.5%; $C_{31}H_{37}N_7O_6.1.5H_2O$ requires C,59.05, H,6.4, N,15.55%.

A portion (0.060g) of a product from a similar reaction was purified by preparative HPLC isocratically at 35% acetonitrile. The faster-running component gave the second (1R) title compound (0.015g) as an off-white solid, MH^+=604, nmr(δ,DMSO-d6;400MHz) includes 1.35(m,1H), 1.55(m,1H), 1.90(m,1H), 2.25(m,1H), 4.30(s,1H), 4.60(br.s,1H), 4.65(m,1H), 5.85(d,1H).

The slower-running component gave the third (1S) title compound (0.015g) as an off-white solid, MH^+=604, nmr(δ,DMSO-d6;400MHz) includes 1.35(m,1H), 1.55(m,1H), 1.90(m,1H), 2.25(m,1H), 4.30(s,1H), 4.60(br.s,1H), 4.65(m,1H), 5.85(d,1H).

EXAMPLE 9

[cis-(+/-)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-[[(phenylmethoxy)carbonyl]amino]cyclopentyl]amino]-N-ethyl-2,3-O-(1-methylethylidene)-9H-purin-9-yl]-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[2,2-(diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.3g,0.533mmol) and [cis-(+/-)]-(3-aminocyclopentyl)carbamic acid phenylmethyl ester (0.41g) was heated at 140°C for 4 days. The cooled mixture was dissolved in dichloromethane and purified by column chromatography on flash silica with 50% ethyl acetate in cyclohexane to give the title compound (0.214g) as a froth, nmr(δ,DMSO-d6) includes 0.55(m,3H), 0.8-1.1(m,2H), 1.1-1.35(m,2H), 1.45(s,3H), 1.5(s,3H), 1.45-1.75(m,2H), 1.75-2.0(m,1H), 2.6-2.95(m,2H), 3.8-4.0(m,1H), 3.95-4.15(m,2H), 4.1-4.3(m,1H), 4.45(s,1H), 4.5-4.65(m,1H), 5.03(m,2H), 5.3-5.5(m,2H), 6.2(bs,1H), 6.45(m,1H), 7.1-7.5(m,15H), 7.78(bs,1H).

EXAMPLE 10

[cis-(+/-)]1-[2-[(3-Aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

A solution of [cis-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-[[(phenylmethoxy)carbonyl]amino]cyclopentyl]amino]-N-ethyl-2,3-O-(1-methylethylidene)-9H-purin-9-yl]-β-D-ribofuranuronamide (0.15g, 0.197mmol) in ethanol (30ml) was hydrogenated over 10% palladium-on-carbon for 8h. The catalyst was removed by filtration and washed with ethanol (20ml) and the combined ethanolic solution was evaporated to leave an oil. The oil was dissolved in ethyl acetate and the solution was filtered before evaporating to an oil. This oil was taken up in trifluoroacetic acid:water (9:1, 5ml) and the solution was left for 3h when the solution was evaporated to leave an oil which was purified by reverse phase HPLC(20-60% acetonitrile) to give the title compound (0.073g) MH^+=587, nmr(δ,DMSO-d6) includes 1.02(t,2H), 1.4-1.65(m,1H), 1.6-1.85(m,2H), 1.85-2.1(m,2H), 3.05-3.25(m,2H), 3.4-3.6(m,1H), 4.0-4.15(m,2H), 4.15-4.22(m,1H), 4.28(s,1H), 4.55-4.7(m,2H), 5.83(d,1H), 7.15-7.4(m,10H), 7.9(bs,3H), 8.15(m,2H).

EXAMPLE 11

[trans-(+/-)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-[[(phenylmethoxy)carbonyl]amino]cyclopentyl]amino]-N-ethyl-2,3-O-(1-methylethylidene)-9H-purin-9-yl]-β-D-ribofuranuronamide, and separation of the diastereoisomers

A mixture of 1-[2-chloro-6-[2,2-(diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.31g, 0.55mmol) and [trans-(+/-)]-(2-aminocyclopentyl)carbamic acid phenylmethyl ester (0.77g, 3.28mmol) was heated at 140°C for 24h. More amine (0.51g, 2.18mmol) was added and the heating continued for a further 17h, then more amine (0.30g, 1.28mmol) was added and the heating (140°C) continued for a further 24h. The cooled mixture was purified by column chromatography on silica with 20% ethyl acetate in cyclohexane, and then by preparative HPLC (50 to 90% acetonitrile) to give the title compound (isomer 1) (0.067g) as a grey foam, MH^+=761, and as the slower-running component, isomer 2 (0.062g) as a grey foam, MH^+=761.

EXAMPLE 12

(trans)-1-[2-[(2-Aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, isomer 1

A solution of [trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-[[(phenylmethoxy)carbonyl]amino]cyclopentyl]amino]-N-ethyl-2,3-O-(1-methylethylidene)-9H-purin-9-yl]-β-D-ribofuranuronamide, isomer 1 (0.075g, 0.098mmol) in ethanol (10ml) was hydrogenated over 10% palladium-on-carbon (10mg) for 2 days. The catalyst was removed by filtration and washed with ethanol and the combined ethanolic solution was evaporated to leave a foam (62mg). The foam (0.058g) was treated with trifluoroacetic acid (0.75ml) and water (0.25ml) and the solution was left for 1.5h. It was then evaporated to a yellow foam (0.076g) which was purified by preparative HPLC(20-60% acetonitrile) to give the title compound (0.030g), MH^+=587, nmr(δ,DMSO-d6) 1.00(t,3H), 1.65(m,4H), 2.15(m,2H), 3.15(m,2H), 3.45(m,1H), 4.00 to 4.35(m,5H), 4.55(m,2H), 5.85(d,1H), 7.00(m,1H), 7.15 to 7.40(m,10H), 7.90 to 8.25(m,5H).

Similarly prepared was:

(trans)-1-[2-[(2-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, isomer 2, from the isomer 2 product of Example 11 (0.072g), which gave 0.065g of product from hydrogenolysis. 0.058g of this was treated with aqueous trifluoroacetic acid as above to give 0.031g of required product, MH^+=587, nmr(δ,DMSO-d6) 1.00(t,3H), 1.65(m,4H), 2.15(m,2H), 3.15(m,2H), 3.45(m,1H), 4.00 to 4.30(m,5H), 4.55(m,2H), 5.90(d,1H),7.15 to 7.40(m,10H), 7.65(m,1H), 8.00(m,2H), 8.20(m,2H).

EXAMPLE 13

[trans-(+/-)]1-[2-[(3-Aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[2,2-(diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.25g,0.44mmol) and [trans-(+/-)]-(3-aminocyclopentyl)carbamic acid phenylmethyl ester (0.29g) were heated for 2 days at 135°C. More amine (0.376g) was then added and the heating was continued for a further 24h. Dichloromethane was added to the cooled mixture which was then purified by column chromatography on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (100:8:1) to give

[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-[[(phenylmethoxy)carbonyl]amino]cyclopentyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.101g). This compound (0.101g, 0.133mmol) in ethanol (10ml) was hydrogenated over 10% palladium-on-carbon (0.05g) for 6h. The catalyst was removed by filtration, washed with ethanol (20ml) and the combined ethanolic solution was evaporated to leave an oil (0.081g) which was dissolved in trifluoroacetic acid:water (95:5, 5ml) and the solution was left for 3h before evaporating to an oil. The oil was purified by reverse phase HPLC (30-70% acetonitrile) to give the title compound (0.042g) as a solid from ether MH^+=587, nmr(δ,DMSO-d6) includes 1.02(t,2H), 1.47-1.7(m,2H), 1.85-2.05(m,1H), 2.0-2.25(m,2H), 3.05-3.25(m,2H), 3.6-3.75(m,1H), 4.0-4.15(m,2H), 4.18(bs,2H), 4.25(s,1H), 5.85(d,1H), 7.15-7.4(m,12H), 7.82(m,3H), 8.15(m,2H).

EXAMPLE 14

[1S-trans]-1-[2-[(3-Aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide and [1R-trans]-1-[2-[(3-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

A solution of [trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-[[(phenylmethoxy)carbonyl]amino]cyclopentyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.601g,0.79mmol) in methanol (50ml) was stirred under nitrogen and heated at reflux with ammonium formate (0.25g). After 3h the cooled mixture was filtered and the filtrate was evaporated to leave [trans-(+/-)]-1-[2-[(3-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.511g) as a solid.

A portion (0.31g) was purified by reverse phase HPLC (38% acetonitrile) and the two products were collected and evaporated to leave Isomer I (0.1g) and Isomer II (0.103g). These were separately treated with trifluoroacetic acid/water 9/1 (5ml) and left for 2.5h. The resulting solutions were evaporated to dryness and the residues were purified by reverse phase HPLC (20-60% acetonitrile) to give the title compounds as solids from ether: Isomer I (0.065g) MH^+=587, nmr(δ,DMSO-d6) includes 1.02(t,3H), 1.45-1.7(m,2H), 1.85-2.25(m,3H), 3.05-3.25(m,2H), 4.15(m,1H), 4.27(s,1H), 4.63(m,2H), 5.84(d,1H), 7.15-7.4(m,10H),

7.84(m,2H), 8.05-8.2(m,2H). Isomer II (0.61g) MH^+=587, nmr(δ,DMSO-d6) 1.02(t,3H), 1.5-1.7(m,2H),, 1.85-2.25(m,3H), 3.05-3.25(m,2H), 4.17(bs,1H), 4.25(s,1H), 4.62(m,2H), 5.84(d,1H), 7.15-7.4(m,10H), 7.84(m,2H), 8.05-8.2(m,2H).

EXAMPLE 15

[trans-(+/-)]-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-[(trifluoroacetyl)amino]cyclopentyl]amino]-N-ethyl-9H-purin-9-yl]-β-D-ribofuranuronamide

Trifluoroacetic anhydride (3 x 0.047ml) was added in three portions over 2h to a stirred mixture of [trans-(+/-)]-1-[2-[(3-aminocyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (the initially formed product from Example 14) (0.2g,0.32mmol) and triethylamine (0.15ml) in dichloromethane (10ml). After a further 0.5h the reaction was diluted with ethyl acetate (50ml) and washed with water (3x20ml), dried ($MgSO_4$) and evaporated to leave an oil which was dissolved in trifluoroacetic acid:water (9:1, 10ml). The solution was left for 2.5h then evaporated to leave an oil which was purified by reverse phase HPLC (30-70% acetonitrile) to give the title compound (0.04g) MH^+=683, nmr(δ,DMSO-d6) includes 1.05(t,3H), 1.4-1.7(m,2H), 1.7-2.0(m,1H), 1.9-2.3(m,3H), 3.1-3.3(m,2H), 4.05-4.3(m,2H), 4.32(m,1H), 4.5-4.7(m,2H), 5.87(d,1H), 7.15-7.4(m,10H), 7.95(s,1H).

EXAMPLE 16

[(trans)-(+/-)]-1-Deoxy-1-[2-[[3-(N,N-dimethylamino)cyclopentyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[2,2-(diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.28g,0.5mmol) and [trans-(+/-)]-3-(N,N-dimethylamino)cyclopentylamine (0.36g,2.81mmol) in dimethylsulphoxide (2ml) was heated at 130°C using a reflux condenser. After 24h the mixture was cooled and partitioned between ethyl acetate (50ml) and water (50ml). The aqueous phase was extracted with ethyl acetate (20ml) and the combined organic solution was evaporated to leave an oil (0.592g) which was purified by column chromatography on flash silica eluting with

dichloromethane:ethanol:0.880 ammonia (100:8:1) to give the title compound (0.163g) as a solid, nmr(δ,$CDCl_3$) includes 0.7(t,3H), 1.48(s,3H), 1.6(s,3H),1.2-1.4(m,1H), 1.45-1.7(m,2H), 1.95(m,2H), 2.05(m,2H), 2.3(s,3H), 2.4(s,3H), 2.75-3.0(m,2H), 2.85-3.1(m,1H), 4.1-4.3(m,1H), 2.25-4.5(m,2H), 4.63(s,1H), 4.78(m,1H), 5.5(m,2H), 5,6(d,1H), 6.0(bs,2H), 7.15-7.35(m,10H), 7.4(s,1H).

EXAMPLE 17

[(trans)-(+/-)]-1-Deoxy-1-[2-[[3-(N,N-dimethylamino)cyclopentyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of [(trans)-(+/-)]-1-deoxy-1-[2-[[3-(N,N-dimethylamino)cyclopentyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.15g,0.23mmol) in trifluoroacetic acid:water (9:1, 10ml) was left at room temperature for 2.5h then evaporated to leave an oil which was purified by reverse phase HPLC (30-70% acetonitrile) to give the title compound (0.12g) as a solid from ether, MH^+=615, nmr(δ,DMSO-d6) includes 1.0(t,3H), 1.55-1.7(m,2H), 1.95-2.25(m,4H), 2.78(s,6H), 3.12(m,2H), 3.7(m,1H), 4.1(m,2H), 4.18(m,1H), 4.28(s,1H), 4.4(m,1H), 4.6(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 7.72(m,1H), 8.15(bs,2H), 9.62(m,1H).

EXAMPLE 18

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.25g,0.444mmol) and histamine (0.35g,3.15mmol) in dimethylsulphoxide (2ml) was heated at 130°C for 18h under nitrogen. The cooled mixture was diluted with ethyl acetate (50ml) and washed with water (2x50ml), dried ($MgSO_4$) and evaporated to leave a froth which was purified by column chromatography on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (100:8:1) to give the title compound (0.176g) as a solid from ether, nmr(δ,$CDCl_3$) includes 0.4(t,3H), 1.35(s,3H), 1.6(s,3H), 2.65-2.9(m,1H), 2.8-3.05(m,3H), 3.4-3.8(m,3H), 4.05-4.3(bs,2H), 4.32(t,1H), 4.7(s,1H), 4.95(m,1H), 4.98(m,1H), 5.5(d,1H), 5.72(dd,1H), 5.97(m,1H), 6.02(s,1H), 6.9(s,1H), 7.15-7.45(m,10H), 7.43(s,1H), 7.62(s,1H).

EXAMPLE 19

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.126g,0.198mmol) in trifluoroacetic acid:water (9:1, 8ml) was left for 3h at room temperature before evaporating to dryness. The resulting oil was treated with ether (20ml) to give the title compound (0.147g) as a solid MH^+=598, nmr(δ,DMSO-d6) includes 0.98(t,3H), 2.9-3.05(m,2H), 3.05-3.25(m,2H), 4.3(s,1H), 4.5-4.65(m,2H), 5.84(d,1H), 7.15-7.35(m,10H), 7.42(s,1H), 8.1(s,1H), 9.0(s,1H), 14.0-14.2(m,2H).

EXAMPLE 20

(1S)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

(S)-Phenylalaninol (0.403g,2.67mmol) and 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.25g,0.44mmol) were heated together for 40h at 130°C. The cooled mixture was purified by column chromatography on flash silica eluting with 10-85% ethyl acetate in cyclohexane to give the title compound (0.136g) as a froth, nmr(δ,$CDCl_3$) includes 0.6(t,3H), 1.4(s,3H) and 1.58(s,3H), 2.7-2.85(m,2H), 2.85-3.0(m,2H), 3.47(dd,1H), 3.81(dd,1H), 4.1-4.5(m,3H), 4.62(s,1H), 5.3(d,1H), 5.69(d,1H), 5.94(s,1H), 7.1-7.4(m,16H).

Similarly prepared were:

1) [cis-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using [cis-(+/-)]-2-aminocyclopentanol[1] as the nucleophile as in entry 1 in Table 1 below. The product was purified on silica eluting with ethyl acetate:cyclohexane (19:1).MH^+=628.

1. R.A.B.Bannard et al., Canad.J.Chem., 1971, 49, 2064

2) [trans-(+/-)]-2-[[6-[(2,2-Diphenylethyl)amino]-9-[N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]amino]cyclopentanecarboxylic acid 2,2-dimethylethyl ester, using (+/-)-trans-2-aminocyclopentanecarboxylic acid 1,1-dimethylethyl ester[1] as the nucleophile as in entry 2 in Table 1 below. The product was purified on silica eluting with ethyl acetate:cyclohexane (4:1).

1. J.Xie, et al., Int.J.Pept.Protein Res., 1989, 34, 246

3) (trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using trans-4-aminocyclohexanol (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 3 in Table 1 below. The product was purified on silica eluting with ethyl acetate:methanol 25:1.MH^+=642.

4) (cis)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using cis-4-aminocyclohexanol[1] (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 4 in Table 1 below. The product was purified on silica eluting with ethyl acetate.MH^+=642.

1. A.G.Renwick and R.T.Williams, Biochem.J., 1972, 129, 857

5) 1-deoxy-N-ethyl-1-[2-[(3-hydroxypropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 3-aminopropanol as the nucleophile as in entry 5 in Table 1 below. The product was purified on silica eluting with dichloromethane:methanol (19:1).MH^+=642.

6) 1-[2-[(4-aminophenyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 1,4-phenylenediamine as the nucleophile as in entry 6 in Table 1 below. The product was purified (twice) on flash silica eluting with ethyl acetate:ethanol (24:1) and then with dichloromethane:methanol (24:1) to give a still impure product.nmr(δ,$CDCl_3$) includes 6.60(d,2H), 6.70(br.s,2H).

7) 1-deoxy-1-[2-[[4-(dimethylamino)phenyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 4-amino-N,N-dimethylaniline as the nucleophile as in entry 7 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:methanol (24:1), nmr(δ,$CDCl_3$) includes 2.80(s), 2.90(s), 6.60 to 6.70(m).

8) (1α,2β,5β)-1-deoxy-1-[2-[[2,5-dihydroxycyclopentyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using [(1α,2β,3α)-(+/-)]-2-amino-1,3-cyclopentanediol (Preparation 33) as the nucleophile as in entry 8 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:methanol (9:1), nmr(δ,DMSO-d6) includes 1.60(br.s), 1.85(br.s), 3.8 to 4.2(2m).

9) (1R-trans)-1-[2-[(2-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (1R-trans)-1,2-diaminocyclohexane as the nucleophile as in entry 9 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:methanol (9:1). MH^+=641.3.

10)(1S-trans)-1-[2-[(2-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (1S-trans)-1,2-diaminocyclohexane as the nucleophile as in entry 10 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:methanol (9:1). MH^+=641.

11)[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[4-hydroxy-1-[(1,1-dimethylethoxy)carbonyl]pyrrolidin-3-yl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using [trans-(+/-)]-3-amino-4-hydroxy-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester as the nucleophile as in entry 11 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (100:8:1). nmr(δ,DMSO-d6) includes 0.55(t,3H), 1.35(s,3H), 1.42(s,9H), 1.5(s,3H), 2.75(m,2H), 3.2(m,1H) 3.4-3.7(m,3H), 3.9-4.3(4H) 4.45(s,1H), 4.6(m,1H), 5.1-5.6(m,4H), 6.15(m,1H), 7.1-7.4(m,12H)7.8(bs,1H).

12)(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(N-ethylpiperidin-3-yl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (+/-)-1-ethyl-3-piperidinamine as the nucleophile as in entry 12 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (100:8:1). nmr(δ,$CDCl_3$) includes 0.75(m,3H), 1.05(m,3H), 2.2-2.6(m,6H), 2.75-3.2(m,3H), 4.0-4.25(m,1H), 4.2(m,2H), 4.35(m,1H), 4.63(s,1H), 5.5(m,3H), 5.95(m,1H), 7.15-7.4(m,10H), 7.4(s,1H).

13)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-piperidinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 1-(2-aminoethyl)piperidine as the nucleophile as in entry 13 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (100:8:1). nmr(δ,$CDCl_3$) includes 0.7(t,3H), 1.4(s,3H), 1.6(s,3H), 1.6-1.9(m,2H), 2.8-3.1(m,2H), 3.12(t,2H), 3.8(m,2H), 4.22(m,2H), 4.85(t,1H), 4.65(s,1H), 5.38(m,1H), 5.0(m,1H), 5.1(m,1H), 5.97(s,1H), 7.1-7.35(m,12H), 7.4(s,1H), 7.6(dt,1H), 8.58(d,1H).

14)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(4-morpholinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 4-(2-aminoethyl)morpholine as the nucleophile as in entry 14 in Table 1 below. The product was purified on flash silica eluting with 0-2% ethanol in ethyl acetate. nmr(δ,$CDCl_3$) includes 0.7(t,3H), 1.4(s,3H), 1.6(s,3H), 2.5(m,4H), 2.6(t,2H), 2.8-3.05(m,2H), 3.4-3.55(m,2H), 3.73(m,4H), 4.15-4.25(m,2H), 4.33(t,1H), 4.63(bs,1H), 5.27(m,1H), 5.48(m,1H), 5.6(m,1H), 5.98(s,1H), 7.15-7.35(m,10H), 7.4(s,1H).

15)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-pyridinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 2-(2-aminoethyl)pyridine as the nucleophile as in entry 15 in Table 1 below. The product was purified on flash silica eluting with ethyl acetate. nmr(δ,$CDCl_3$) includes 0.68(t,3H), 1.37(s,3H), 1.6(s,3H), 1.6-1.9(m,2H), 2.75-3.1(m,2H), 3.13(t,2H), 3.7-3.95(m,2H), 4.0-4.4(m,2H), 4.38(t,1H), 4.65(s,1H), 5.28(m,1H),

5.5(m,2H), 5.6(m,1H), 5.98(s,1H), 6.12(m,1H), 7.1-7.4(m,12H), 7.4(s,1H), 7.6(dt,1H), 8.57(d,,1H).

16)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(pyrrolidin-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 1-(2-aminoethyl)pyrrolidine as the nucleophile as in entry 16 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (100:8:1). nmr(δ,$CDCl_3$) includes 0.63(t,3H), 1.4(s,3H), 1.6(s,3H), 2.0(m,4H), 2.7-3.0(m,2H), 2.9-3.5(m,4H), 3.6-3.9(m,2H), 4.1-4.3(m,2H), 4.32(t,1H), 4.63(s,1H), 5.4-5.65(m,4H), 5.8-6.1(m,1H), 6.05(s,1H), 7.15-7.4(m,10H), 7.45(s,1H).

17)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-pyridinyl)methyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 2-(aminomethyl)pyridine as the nucleophile as in entry 17 in Table 1 below. The product was purified on flash silica eluting with ethyl acetate. nmr(δ,DMSO-d6) includes 0.52(t,3H), 1.12(bs,3H), 1.45(s,3H), 2.6-2.9(m,2H), 3.8-4.1(m,2H), 4.3-4.6(m,3H), 4.42(s,1H), 4.75-4.9(m,1H), 5.12(m,1H), 5.88(m,1H), 6.15(s,1H), 7.0-7.5(m,12H), 7.6-7.9(m,3H), 8.5(d,1H).

18)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(4-pyridinyl)methyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 4-(aminomethyl)pyridine as the nucleophile as in entry 18 in Table 1 below. The product was purified on flash silica eluting with ethyl acetate. nmr(δ,$CDCl_3$) includes 0.65(t,3H), 1.35(s,3H), 1.52(s,3H), 1.8-2.1(m,2H), 2.75-3.05(m,2H), 4.0-4.25(m,2H), 4.38(t,1H), 4.35-4.5(dd,1H), 4.6(s,1H), 4.75-4.95(dd,1H), 5.17(d,1H), 5.3-5.5(m,2H), 5.55-5.7(m,1H), 5.92(m,1H), 5.94(s,1H), 7.15-7.35(m,12H), 7.4(s,1H), 8.5(m,2H).

19)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[(1H-imidazol-2-yl)methyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 2-(aminomethyl)imidazole[1] (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 19 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (200:8:2) to (150:8:1.5). nmr(δ,$CDCl_3$) includes 0.54(t,3H), 1.4(s,3H),

1.59(s,3H), 2.55-2.95(m,2H), 4.05-4.2(m,2H), 4.25-4.34(m,1H), 4.4-4.5(m,1H), 4.9-5.1(m,1H), 4.7(s,1H), 5.61(d,1H), 5.78(dd,1H), 6.03(s,1H), 7.02(s,2H), 7.15-7.35(m,10H), 7.45(s,1H).

1. L.A.M.Bastiaansen and E.F.Godefroi, J.Org.Chem., 1978, 43(8), 1603

20)4-[2-[[6-[(2,2-diphenylethyl)amino]-9-[N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]amino]ethyl]benzenepropanoic acid 1,1-dimethylethyl ester, using 3-[4-(2-aminoethyl)phenyl]propionic acid 1,1-dimethylethyl ester[1] as the nucleophile as in entry 20 in Table 1 below. The product was purified on flash silica eluting with 20-40% ethyl acetate in cyclohexane. nmr(δ,$CDCl_3$) includes 0.67(t,3H), 1.38(s,3H), 1.43(s,9H), 1.6(s,3H), 2.52(t,2H), 2.75-3.05(m,6H), 3.5-3.8(m,2H), 4.1-4.3(m,2H), 4.35(t,1H), 4.63(s,1H), 4.9(m,1H), 5.48(m,2H), 5.6(d,1H), 5.97(s,1H), 7.12(m,4H), 7.15-7.35(m,10H),7.4(s,1H).

1. A.J.Hutchison et al., J.Med.Chem., 1990, 33, 1919

21)(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-(3-pyridinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (S)-β-amino-3-pyridinepropanol (prepared by basification of the dihydrochloride salt) as the nucleophile as in entry 21 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (200:8:2). MH^+=679.

22)(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-(methyl)propyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using (S)-(+)-2-amino-3-methyl-1-butanol as the nucleophile as in entry 22 in Table 1 below. The product was purified on flash silica eluting with 50% ethyl acetate in cyclohexane to neat ethyl acetate. MH^+=630.

23)[cis-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using [cis-(+/-)]-3-aminocyclopentanol[1] as the nucleophile as in entry 23 in Table 1 below. The product was purified by column chromatography on flash silica eluting with dichloromethane:ethanol:0.880

ammonia (100:8:1). nmr(δ,$CDCl_3$) includes 0.68 and 0.7(t,3H), 1.38(s,3H), 1.6(s,3H), 1.65-1.85(m,4H), 1.8-2.0(m,2H), 1.9-2.3(m,2H), 2.7-2.95 and 2.9-3.1(m,2H), 4.1-4.35(m,2H), 4.3-4.5(m,3H), 4.6(m,1H), 5.25 and 5.37(d,1H), 5.45-5.6(m,2H), 5.97(s,1H), 7.15-7.35(m,10H), 7.4(s,1H).

1. R.A.B.Bannard,et al., Canad.J.Chem., 1971, 49, 2064

24)(1S)-1-deoxy-1-[2-[1-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]-2-phenylethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using (S)-(2-amino-3-phenylpropyl)carbamic acid 1,1-dimethylethyl ester (Preparation 53) as the nucleophile as in entry 24 in Table 1 below. The product was purified on flash silica eluting with 40-45% ethyl acetate in toluene. MH^+=777.

25)1-deoxy-1-[2-[[2-(N,N-dimethylamino)ethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using 2-(N,N-dimethylamino)ethylamine as the nucleophile as in entry 25 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (100:8:1). MH^+=615.

26)1-deoxy-1-[2-[[3-(N,N-dimethylamino)propyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using 3-(N,N-dimethylamino)propylamine as the nucleophile as in entry 26 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (100:8:1). MH^+=629.

27)(+1-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(5-oxo-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using (+/-)-4-amino-1H-pyrrolidin-2-one (prepared by basification of the hydrochloride salt) (Preparation 26) as the nucleophile as in entry 27 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (200:8:1) to (100:8:1). nmr(δ,$CDCl_3$) includes 0.6-0.7(m,3H), 1.4(s,6H), 2.8-3.0(m,2H), 3.3-3.4 and 3.75-3.9(m,22H), 4.0-4.35(m,3H), 4.65(s,1H), 4.7-4.8(m,1H), 5.4-5.7(m,2H), 6.01(d,1H), 7.2-7.4(m,10H), 7.45-7.5(bs,1H).

28)1-deoxy-1-[6-[(2,2-diphenyl thyl)amino]-2-[[1-hydroxymethyl)cyclopropyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using 1-amino-cyclopropanemethanol (Preparation 23) as the nucleophile as in entry 28 in Table 1 below. The product was purified on flash silica eluting with 50% ethyl acetate in cyclohexane to neat ethyl acetate. MH^+=614.

29)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-piperazinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using 1-(2-aminoethyl)piperazine as the nucleophile as in entry 29 in Table 1 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.88ammonia (100:8:1). nmr(δ,$CDCl_3$) includes 0.7(t,3H), 1.35(s,3H), 1.6(s,3H), 2.4-2.7(m,6H), 2.87(t,2H), 2.8-3.1(m,2H), 3.25-3.6(m,2H), 3.65-3.9(m,4H), 4.1-4.3(m,2H), 4.35(m,1H), 4.62(s,1H), 5.4-5.7(m,1H), 5.55(s,2H), 5.85-6.05(m,1H), 6.0(s,1H), 7.15-7.35(m,10H), 7.4(s,1H).

30)[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using [trans-(+/-)] 2-aminocyclohexanol (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 30 in Table 1 below. The product was purified on silica eluting with ethyl acetate:cyclohexane (2:1).MH^+=642.

31)(1α,3β,4β)-1-deoxy-1-[2-[(3,4-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (1α,2α,4β) 4-amino-1,2-cyclopentanediol (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 31 in Table 1 below. The product was purified on silica eluting with ethyl acetate:methanol (24:1). nmr(δ,DMSO-d6) includes 1.60(br.s,2H), 1.82(br.s,2H), 4.0(br.s).

32)1-[2-[(2-cyclohexylethyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 2-cyclohexylethylamine as the nucleophile as in entry 32 in Table 1 below. The product was purified on silica eluting with ethyl acetate:cyclohexane (1:1).

nmr(δ,$CDCl_3$) includes 0.7(t,3H), 0.8-1.1(m,2H), 1.1-1.5(m,4H), 1.4(s,3H), 1.45-1.55(m,1H), 1.6(s,3H), 1.5-1.8(m,6H), 2.8-3.1(m,2H), 3.2-3.45(m,1H), 3.35-3.6(m,1H), 4.1-4.3(m,2H), 4.35(t,1H), 4.63(s,1H), 4.8(m,1H), 5.5(m,1H), 5.6(d,1H), 5.97(s,1H), 6.05(m,1H), 7.15-7.35(m,10H), 7.4(s,1H).

33)(1R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (R)-2-amino-3-phenyl-1-propanol as the nucleophile as in entry 33 in Table 1 below. The product was purified on silica eluting with 50% ethyl acetate in cyclohexane to neat ethyl acetate. MH^+=678.

34)(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(methoxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (S)-2-amino-1-methoxy-3-phenylpropane (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 34 in Table 1 below. The product was purified on silica eluting with 50-70% ethyl acetate in cyclohexane. MH^+=692.

35)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-methyl-1H-imidazol-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 2-(2-methyl-1H-imidazol-1-yl)ethylamine (prepared by basification of the hydrochloride salt[1]) as the nucleophile as in entry 35 in Table 1 below. The product was purified on silica with gradient elution of 1 - 8% methanol in dichloromethane and addition of ether to the resulting oil gave a solid. nmr(δ,$CDCl_3$) includes 0.65(t,3H), 1.4(s,3H), 1.6(s,3H), 2.35(s,3H), 2.7-3.05(m,2H), 3.6-3.8(m,2H), 4.05-4.25(m,3H), 4.3(t,1H), 4.67(s,1H), 4.85-5.0(m,1H), 5.43(d,,1H), 5.45-5.15(m,1H), 5.63(dd,1H), 5.9-6.0(m,1H), 6.03(s,1H), 6.86(bs,1H), 7.15-7.4(m,10H), 7.45(s,1H).

1. Shikoku Kaken Kogyo K.K., Japanese Patent 62,198,668.

36)[(1S)-trans]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-N,N-dimethylamino)cyclopentylamino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using (S)-3-(N,N-dimethylaminocyclopentyl)amine (prepared by basification of the hydrochloride salt) as the nucleophile as in entry 36 in Table 1 below. The product was

purified on silica eluting with dichloromethane:ethanol:0.88 ammonia (100:8:1) to (50:8:1) and preparative HPLC (30-90% acetonitrile). MH^+=655.

37)1-[2-[[(6-Amino-2-pyridinyl)methyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide using 6-amino-2-pyridinemethanamine as the nucleophile as in entry 37 in Table 1 below. The product was purified on silica eluted with ethyl acetate and the addition of ether to the resulting oil gave a solid. nmr (δ, $CDCl_3$) includes 0.7 (t,3H), 1.35 (s,3H), 1.58 (s,3H), 2.85 - 3.15 (m,2H), 4.1 - 4.3 (m,2H), 4.3 - 4.4 (t,1H), 4.45 (bs,2H), 4.45 - 4.6 (m,2H), 4.65 (d,1H), 5.4 (d,1H), 5.56 (d,1H), 5.95 (s,1H), 6.36 (d,1H), 6.7 (d,1H), 7.15 - 7.35 (m,10H), 7.35 (t,1H), 7.42 (s,1H).

TABLE 1

Entry	2-chloropurine g.	nucleophile g.	DMSO ml	temp. °C	reaction time
1	0.239	0.43	nil	140	18h
2	0.061	0.10	0.40	140	48h
3	0.371	1.0 (HCl salt)	nil	140	8h
4	0.180	0.48(HCl salt)	0.5	140	7h
5	0.30	0.398	1.5	140	1.5h
6	0.2275	0.510	nil	140	48h
7	0.200	0.440	0.8	140	24h
8	0.185	0.185	nil	140	48h
9	0.105	0.226	nil	140	3h
10	0.104	0.213	nil	140	4.5h
11	0.32	0.4	1.5	135	48h
12	0.26	0.577	nil	120	18h
13	0.261	0.577	nil	120	18h
14	0.286	1.03	nil	120	4.5h
15	0.257	0.42	2.0	130	18h
16	0.284	0.82	nil	120	4.5h
17	0.2	0.2	nil	130	18h
18	0.202	0.192	nil	120	26h

19	0.321	0.58(HCl salt)	nil	130	48h
20	0.252	0.623	2.0	130	18h
21	0.25	0.3(HCl salt)	1.0	140	312h
22	0.322	0.354	1.0	120	77h
23	0.250	0.13	nil	135	72h
24	0.3	0.8	1.0	125	156h
25	0.304	0.286	1.0	130	4h
26	0.304	0.331	1.0	130	4h
27	0.3	0.36(HCl salt)	1.0	140	192h
28	0.3	0.232	1.0	140	207h
29	0.27	1.0	2.0	130	18h
30	0.249	1.31(HCl salt)	nil	140	44h
31	0.083	0.113	nil	120	18h
32	0.252	0.340	2.0	130	48h
33	0.250	0.403	nil	130	73h
34	0.325	0.75(HCl salt)	1.0	130	96h
35	0.320	0.88(HCl salt)	2.5	130	41h
36	1.306	0.47(HCl salt)	4.0	130	47h
37	0.260	0.32	2.0	110	60h

EXAMPLE 21

(1S)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of (1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.104g,0.16mmol) in trifluoroacetic acid (4.7ml) and water (0.3ml) was stirred for 3.5h then evaporated to dryness. The residue was dissolved in ethanol (10ml) and the solution was stirred with sodium carbonate (1g) for 0.7h. The mixture was filtered and the filtrate was evaporated to leave a froth which was dissolved in ethyl acetate (50ml) and washed with water (40ml), dried ($MgSO_4$) and evaporated to give the title compound (0.082g) as a solid MH^+=638, nmr(δ, DMSO-d6) includes 0.98(t,3H), 2.88(m,2H), 3.05-3.25(m,2H), 3.4-3.5(m,2H), 4.23(s,1H), 5.48(d,1H), 5.6(d,1H), 5.8(d,1H), 7.1-7.4(m,15H)

Similarly prepared were:

1) [cis-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 1 in Example 20 and in Table 1 above, under conditions as in entry 1 in Table 2 below. The product was purified on silica eluting with ethyl acetate:methanol (19:1). The product had MH^+=588, nmr(δ,DMSO-d6) 1.05(t,3H), 1.35 to 1.90(m,6H), 3.15(m,2H), 4.05(m,4H), 4.25(s,1H), 4.65(m,2H), 4.85(d,1H), 5.50(d,1H), 5.65(t,2H), 5.80(d,1H), 7.10 to 7.40(m,11H), 7.50(m,1H), 7.90(s,1H), 8.55(m,1H).

2) [trans-(+/-)]-2-[[6-[(2,2-diphenylethyl)amino]-9-(N-ethyl-β-D-ribofuranuronamidosyl)-9H-purin-2-yl]amino]cyclopentanecarboxylic acid, from the product as in entry 2 in Example 20 and in Table 1 above, under conditions as in entry 2 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=616, nmr(δ,DMSO-d6) 1.00(t,3H), 1.70(m,4H), 2.05(m,2H), 2.80(m,1H), 3.15(m,2H), 4.10(m,3H), 4.30(s,1H), 4.60(m,4H), 5.85(d,1H), 7.15 to 7.40(m,10H), 8.25(m,2H).

3) (trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 3 in Example 20 and in Table 1 above, under conditions as in entry 3 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=602. Analysis found C,52.7, H,5.15, N,11.8, F,11.8%; $C_{32}H_{39}N_7O_5.1.75CF_3CO_2H.0.4H_2O$ requires C,52.7, H,5.2, N,12.1, F,12.3%.

4) (cis)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 4 in Example 20 and in Table 1 above, under conditions as in entry 4 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=602. Analysis found C,53.35, H,5.65, N,11.8, F,9.9%; $C_{32}H_{39}N_7O_5.1.4CF_3CO_2H.0.9H_2O$ requires C,53.75, H,5.5, N,11.6, F,10.25%.

5) 1-deoxy-N-ethyl-1-[2-[(3-hydroxypropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-β-D-ribofuranuronamide, from the product as in entry 5 in Example 20 and in Table 1 above, under conditions as in entry 5 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=562. Found C,52.75, H,5.1, N,13.65, F,9.9%. $C_{29}H_{35}N_7O_5.1.25CF_3CO_2H.0.6H_2O$ requires C,52.95, H,5.3, N,13.7, F,10.0%.

6) 1-[2-[(4-aminophenyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 6 in Example 20 and in Table 1 above, under conditions as in entry 6 in Table 2 below. The product was purified on flash silica (twice) eluting with dichloromethane:methanol (9:1). The product had MH^+=594, nmr(δ,DMSO-d6) includes 6.50(d,2H), 7.28 to 7.48(m,12H)

7) 1-deoxy-1-[2-[[4-(dimethylamino)phenyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 7 in Example 20 and in Table 1 above, under conditions as in entry 7 in Table 2 below. The product was purified twice by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=623, nmr(δ,DMSO-d6) includes 2.95 to 3.2(br.s,6H), 7.15 to 7.25(m,2H), 7.75 to 7.9(m,2H).

8) (1α,2β,5β)-1-deoxy-1-[2-[[2,5-dihydroxycyclopentyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 8 in Example 20 and in Table 1 above, under conditions as in entry 8 in Table 2 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (30:8:1) and then on flash silica eluting with ethyl acetate:methanol (19:1). The product had MH^+= 604, nmr(δ,DMSO-d6) includes 1.67(br.s,2H), 1.90(br.s,2H), 4.0(br.s,2H).

9) (1R-trans)-1-[2-[[2-aminocyclohexyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 9 in Example 20 and in Table 1 above, under conditions as in entry 9 in Table 2 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (30:8:1). The product had MH^+= 601, nmr(δ,DMSO-d6) includes 1.23(br.s,6H), 1.68(br.s,2H), 2.92(br.s,1H).

10)(1S-trans)-1-[2-[[2-aminocyclohexyl]amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 10 in Example 20 and in Table 1 above, under conditions as in entry 10 in Table 2 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (30:8:1). The product had MH^+= 601, nmr(δ,DMSO-d6) includes 1.24(br.s,6H), 1.64(br.s,2H), 2.66(br.s,1H).

11)[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-(4-hydroxy-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 11 in Example 20 and in Table 1 above, under conditions as in entry 11 in Table 2 below. The product was purified by preparative HPLC (20 to 60% acetonitrile). The product had MH^+= 589, nmr(δ,DMSO-d6) includes 1.0(t,3H), 3.0-3.25(m,3H), 3.25-3.6(m,3H), 4.1(m,2H), 4.15(m,1H), 4.25(s,1H), 4.25-4.5(m,2H), 4.6(m,2H), 5.85(d,1H), 7.1-7.4(10H), 8.14(m,2H).

12)(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(N-ethylpiperidin-3-yl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 12 in Example 20 and in Table 1 above, under conditions as in entry 12 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=615, nmr(δ,DMSO-d6) includes 1.0(t,3H)1.2(m,3H), 1.5-2.2(m,4H), 2.4-2.9(m,2H), 3.05-3.25(m,4H), 4.15(m,1H), 4.25(bs,1H), 4.5-4.7(m,2H), 5.87(m,1H), 7.15-7.4(m,10H), 8.12(m,2H).

13)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-piperidinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 13 in Example 20 and in Table 1 above, under conditions as in entry 13 in Table 2 below. The product was isolated by evaporation of the reaction mixture and the addition of ether to give a solid. The product had MH^+=615, nmr(δ,DMSO-d6) includes 1.02(t,3H), 1.25-1.5(m,1H), 1.5-1.85(m,4H), 2.9(m,1H), 3.14(m,1H), 3.22(m,1H), 3.5(m,1H), 3.65(m,1H), 4.07(m,2H),4.2(m,1H), 4.28(s,1H), 4.6(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 8.15(m,2H).

14)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(4-morpholinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 14

in Example 20 and in Table 1 above, under conditions as in entry 14 in Table 2 below. The product was isolated by evaporation of the reaction mixture and the addition of ether to give a solid. The product had MH^+=617, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.14(m,4H), 3.45(m,4H), 4.25(s,1H), 4.55(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 8.15(bs,2H).

15)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-pyridinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the product as in entry 15 in Example 20 and in Table 1 above, under conditions as in entry 15 in Table 2 below. The product was isolated by evaporation of the reaction mixture and the addition of ether to give a solid. The product had MH^+=609, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.05-3.25(m,2H), 3.15-3.35(m,2H), 3.7-3.9(m,2H), 4.1(m,1H), 4.2(m,1H), 4.35(s,1H), 4.5-4.7(m,2H), 5.87(d,1H), 7.15-7.4(m,10H), 7.6-7.8(m,2H), 8.1-8.4(m,3H), 8.72(m,1H).

16)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(pyrrolidin-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 16 in Example 20 and in Table 1 above, under conditions as in entry 16 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=601, nmr(δ,DMSO-d6) includes 1.02(t,3H), 1.7-2.1(m,4H), 2.9-3.25(m,4H), 3.35(m,2H), 3.6(m,4H), 4.78(s,1H), 4.55(m,3H), 5.85(d,1H), 7.1-7.4(m,10H), 8.15(bs,2H).

17)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-pyridinyl)methyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 17 in Example 20 and in Table 1 above, under conditions as in entry 17 in Table 2 below. The product was purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (30:8:1). The product had MH^+= 601, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.1-3.3(m,2H), 3.7-4.0(m,2H), 4.15(bs,1H), 4.32(s,1H), 4.4-4.6(m,3H), 4.8(s,1H), 5.85(d,1H), 7.1-7.4(m,10H), 7.65(t,1H), 7.72(d,1H), 8.0-8.5(m,2H), 8.2(s,1H), 8.67(d,1H).

18)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(4-pyridinyl)methyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 18 in Example 20 and in Table 1 above, under conditions as in entry 18 in Table 2

below. The product was purified by preparative HPLC (20 to 60% acetonitrile). The product had MH^+= 601, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.05-3.3(m,2H), 3.75-4.0(m,2H), 4.14(m,1H), 4.25(s,1H), 4.45(m,2H), 4.55(m,1H), 5.82(d,1H), 7.05-7.4(m,10H), 7.85(d,2H), 8.12(s,1H), 8.78(d,2H).

19)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[(1H-imidazol-2-yl)methyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 19 in Example 20 and in Table 1 above, under conditions as in entry 19 in Table 2 below. The product was purified by preparative HPLC (30 to 90% acetonitrile). The product had MH^+=584, nmr(δ,DMSO-d6) includes 1.01(t,3H), 3.08-3.2(m,2H), 3.8-4.3(m,4H), 4.4-4.52(m,2H), 4.72-4.82(m,1H), 5.82(d,1H), 7.15-7.4(m,10H), 7.55(bs,2H), 7.55-7.65(m,1H), 8.1-8.2(m,2H).

20)4-[2-[[6-[(2,2-diphenylethyl)amino]-9-[N-ethyl-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]amino]ethyl]benzenepropanoic acid, from the product as in entry 20 in Example 20 and in Table 1 above, under conditions as in entry 20 in Table 2 below. The product was isolated by evaporation of the reaction mixture and the addition of ethyl acetate to give a solid. The product had MH^+=680, nmr(δ,DMSO-d6) includes 1.02(t,3H), 2.7-2.95(m,4H), 3.05-3.3(m,2H), 3.4-3.7(m,2H), 4.04-4.25(m,3H), 4.35(s,1H), 4.45-4.7(m,2H), 5.88(d,1H), 7.13(s,4H), 7.15-7.4(m,10H), 8.16(bs,1H).

21)(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-(3-pyridinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 21 in Example 20 and in Table 1 above, under conditions as in entry 21 in Table 2 below but using 4M-aqueous hydrogen chloride in 1,4-dioxan for the deprotection. The product was purified by preparative HPLC (20-40% acetonitrile). MH^+= 639, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.9-3.2(m,4H), 4.3(s,1H), 4.5-4.6(m,2H), 5.82(d,1H), 7.15-7.4(m,11H), 7.65-7.75(m,1H), 8.6-8.75(m,2H).

22)(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-(methyl)propyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 22 in Example 20 and in Table 1 above, under conditions as in entry 22 in Table 2 below but using 4M-aqueous hydrogen chloride in 1,4-

dioxan for the deprotection. The product was purified by preparativ HPLC (30-60% acetonitrile) had MH^+= 590, nmr(δ,DMSO-d6) includes 0.9-1.0(m,6H), 1.01(t,3H), 3.1-3.3(m,2H), 3.5-3.6(m,2H), 3.9-4.2(4H), 4.5-4.7(m,2H), 4.23(s,1H), 5.49(d,1H), 5.61(d,1H), 5.75-5.85(m,1H), 7.1-7.4(m,10H), 7.91(s,1H).

23)[cis-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the product as in entry 23 in Example 20 and in Table 1 above, under conditions as in entry 23 in Table 2 below. The product was purified by preparative HPLC (40-80% acetonitrile) and had MH^+=588, nmr(δ, DMSO-d6) includes 1.02(t,3H), 1.4-1.85(m,4H), 1.9-2.3(m,2H), 3.1-3.3(m,2H), 4.0-4.15(m,1H), 4.1-4.3(m,2H), 4.33(s,1H), 4.5-4.7(m,2H), 5.54(d,1H), 7.1-7.4(m,10H), 8.14(bs,1H).

24)(1S)-1-[2-[[1-(aminomethyl)-2-phenylethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide from the product as in entry 24 in Example 20 and in Table 1 above, under conditions as in entry 24 in Table 2 below. The product was purified by preparative HPLC (32 to 40% acetonitrile). The product had MH^+= 637, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.7-2.8(m,2H), 2.9-3.2(m,4H), 4.5-4.65(m,1H), 5.85-5.95(m,1H), 6.55-6.65(m,1H), 7.15-7.4(m,15H), 8.1-8.2(m,2H).

25)1-deoxy-1-[2-[[2-(N,N-dimethylamino)ethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the product as in entry 25 in Example 20 and in Table 1 above, under conditions as in entry 25 in Table 2 below. The product was purified by preparative HPLC (27 to 60% acetonitrile). The product had MH^+=575, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.82(s,3H), 2.83(s,3H), 3.1-3.2(m,2H), 3.2-3.35(m,2H), 3.55-3.7(m,2H), 4.5-4.6(d,1H), 5.85(d,1H), 6.75-6.9(m,1H), 7.15-7.4(m,10H), 8.1-8.2(m,2H).

26)1-deoxy-1-[2-[[3-(N,N-dimethylamino)propyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the product as in entry 26 in Example 20 and in Table 1 above, under conditions as in entry 26 in Table 2 below. The product was purified by preparative HPLC (27

to 54% acetonitrile). The product had MH^+=589, nmr(δ,DMSO-d6) includes 1.01(t,3H), 1.85-2.0(m,2H), 2.75(s,3H), 2.76(s,3H), 3.05-3.2(m,4H), 3.3-3.45(m,2H), 4.5-4.6(m,1H), 5.86(d,1H), 7.15-7.4(m,10H), 8.1-8.25(m,2H).

27)(+/-)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(5-oxo-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 27 in Example 20 and in Table 1 above, under conditions as in entry 27 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=587, nmr(δ,DMSO-d6) includes 1.01(t,3H), 2.2-2.3(m,1H), 2.76-2.8(m,1H), 3.1-3.25(m,3H), 3.58-3.68(m,1H), 5.86(d,1H), 7.3-7.4(m,10H), 7.66(d,1H), 8.15-8.25(bs,1H).

28)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)cyclopropyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 28 in Example 20 and in Table 1 above, under conditions as in entry 28 in Table 2 below but using 4M aqueous hydrogen chloride in 1,4-dioxan for the deprotection. The product was purified by preparative HPLC (30-53% acetonitrile) and had MH^+= 574, nmr(δ,DMSO-d6) includes 0.7-0.9(m,4H), 1.01(t,3H), 3.1-3.25(m,2H), 4.0-4.1 and 4.13-4.2(ms,3H), 4.25-4.3(bs,1H), 4.5-4.7(m,2H), 5.82(d,1H), 7.2-7.4(m,10H), 8.12(bs,1H).

29)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-piperazinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 29 in Example 20 and in Table 1 above, under conditions as in entry 29 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=616, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.0-3.25(m,2H), 3.1-3.45(m,4H), 4.25(s,1H), 4.5-4.7(m,3H), 5.88(d,1H), 7.15-7.4(m,10H), 8.15(s,1H).

30)[trans-(+/-)]-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 30 in Example 20 and in Table 1 above, under conditions as in entry 30 in Table 2 below. The product was purified on flash silica eluting with dichloromethane:methanol:0.880 ammonia (90:10:1). The product had

MH^+=602, nmr(δ,DMSO-d6) includes 1.20(br.s), 1.60(br.s), 1.92(br.s), 2.20(br.s).

31)(1α,3β,4β)-1-deoxy-1-[2-[(3,4-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 31 in Example 20 and in Table 1 above, under conditions as in entry 31 in Table 2 below (as the sum of 2 similar experiments whose products were combined). The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=604, nmr(δ,DMSO-d6) includes 1.69(br.s,2H), 1.90(br.s,2H), 4.0(br.s,2H).

32)1-[2-[(2-cyclohexylethyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide,from the product as in entry 32 in Example 20 and in Table 1 above, under conditions as in entry 32 in Table 2 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=614, nmr(δ,DMSO-d6) includes 0.8-1.0(m,2H), 1.05(t,3H), 1.1-1.4(m,5H), 1.4-1.8(6H), 3.1-3.3(m,2H), 3.3-3.6(m,2H), 4.35(s,1H), 4.45-4.7(m,2H), 5.87(d,1H), 7.15-7.4(10H), 8.2(bs,1H).

33)(1R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the product as in entry 33 in Example 20 and in Table 1 above, under conditions as in entry 33 in Table 2 below. The product had MH^+=638, nmr(δ,DMSO-d6) 1.0(t,3H), 2.9(bd,2H), 3.1-3.25(m,2H), 3.4-3.5(m,2H), 4.0-4.2(m,3H), 4.3(bs,2H), 4.55-4.65(m,2H), 4.75-4.82(m,1H), 5.48(d,1H), 5.59(d,1H), 5.82(bd,1H), 5.95-6.05(m,1H), 7.1-7.4(m,15H), 7.97(bs,1H),

34)(1S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(methoxymethyl)-2-phenylethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 34 in Example 20 and in Table 1 above, under conditions as in entry 34 in Table 2 below. The product was purified by preparative thin layer chromatography eluting with dichloromethane:ethanol:0.88ammonia (150:8:1) (4 passes). The product had MH^+=652, nmr(δ,DMSO-d6) includes 0.97(t,3H), 2.8-2.9(m,2H), 3.0-3.2(m,3H), 3.27(s,3H), 3.4-3.45(m,2H), 4.0-4.1 and 4.1-4.2(m,2H), 4.23(bs,1H), 4.6-4.7(m,2H), 5.8(bd,1H), 7.1-7.4(m,15H), 7.95(bs,1H).

35)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[(2-methyl-1H-imidazol-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product as in entry 35 in Example 20 and in Table 1 above under conditions as in entry 35 in Table 2 below. The product was isolated by the evaporation of the reaction mixture and the addition of ether to give a solid. MH^+=612, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.47(s,3H), 3.0-3.25(m,2H), 3.55-3.8(m,2H), 3.95-4.15(m,2H), 4.2(m,2H), 4.25-4.35(m,2H), 4.5-4.65(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 7.52(s,1H), 7.58(s,1H), 8.12(bs,2H).

36)[(1S)-trans]-1-deoxy-1-[2-[(3-N,N-dimethylamino)cyclopentylamino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the product as in entry 36 in Example 20 and in Table 1 above under conditions as in entry 36 in Table 2 below. The product was purified by preparative HPLC (20-60% acetonitrile).The product had MH^+=615, nmr(δ,DMSO-d6) includes 1.01(t,3H), 1.6-1.8(m,2H), 2.05-2.3(m,4H), 2.75-2.81(m,6H), 3.1-3.2(m,2H), 4.0-4.15m,1H), 4.15-4.22(m,1H), 4.3-4.5(m,1H), 4.25(bs,1H), 4.55-4.67(m,2H), 5.82(d,1H), 7.15-7.4(m,10H), 9.45-9.6(m,1H).

37)1-[2-[[(6-Amino-2-pyridinyl)methyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide from the product as in entry 37 in Example 20 and in Table 1 above under conditions as in entry 37 in Table 2 below. The product was isolated by evaporation of the reaction mixture and the addition of ether to give a solid. The product had MH^+=610, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.05-3.15(m,2H), 4.15(m,1H), 4.28(d,1H), 4.4-4.65(m,4H), 5.84(d,1H), 6.75(d,1H), 6.82(d,1H), 7.1-7.35(10H), 7.83(t,1H), 7.15(s,1H).

TABLE 2

Entry	starting material g.	trifluoroacetic acid, ml	water ml	reaction time
1	0.114	1.0	0.5	3h
2	0.042	0.5	0.1	3h
3	0.161	2.0	0.5	1h

4	0.081	1.0	0.3	1.5h
5	0.197	2.0	0.5	2h
6	0.081	0.9	0.1	2h
7	0.210	2.7	0.3	1h
8	0.154	1.8	0.2	3h
9	0.069	1.0	0.1	2.75h
10	0.033	1.0	0.1	4.75h
11	0.150	9.0	1.0	3.5h
12	0.085	9.0	1.0	3.0h
13	0.120	9.0	1.0	3.0h
14	0.145	9.0	1.0	3.0h
15	0.149	9.0	1.0	3.0h
16	0.160	9.0	1.0	3.0h
17	0.121	11.4	0.6	3.5h
18	0.190	11.4	0.6	5.0h
19	0.117	4.5	0.5	2.0h
20	0.210	9.0	1.0	2.5h
21	0.026	5.0(HCl)	1.0(dioxan)	22h
22	0.111	7.0(HCl)	15(dioxan)	96h
23	0.152	4.5	0.5	3.3h
24	0.126	5.0	0.5	1.0h
25	0.200	9.0	1.0	3.0h
26	0.200	9.0	1.0	3.0h
27	0.054	2.5	0.5	1.0h
28	0.023	5.0(HCl)	3.0(dioxan)	46h
29	0.082	9.0	1.0	3.0h
30	0.042	1.0	0.1	5.75h
31	0.052	0.7	0.35	3.5h
32	0.140	9.0	1.0	2.5h
33	0.122	4.75	0.25	2.5h
34	0.153	5.0	0.5	2.0h
35	0.221	4.5	0.5	3.5h
36	0.038	2.0	0.4	2.0h
37	0.150	8.0	2.0	0.6h

EXAMPLE 22

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-oxocyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of (trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxycyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (Example 20 and Table 1, entry no.3) (0.158g,0.246mmol) in acetone (15ml) was treated dropwise with Jones' reagent (ca 0.5ml) until the red-brown colour persisted, and the reaction was stirred for a further 30 min. at 21°C. 2-Propanol (0.5ml) was then added dropwise to disperse the colour. The mixture was basified to pH 9 with 2N-sodium hydroxide solution, and it was then diluted with water (10ml) and extracted with ethyl acetate (4 x 15ml). The combined organic layers were washed (brine), dried (Na_2SO_4) and evaporated to a foam which was purified on silica eluting with ethyl acetate:cyclohexane (9:1) to give the title compound (102mg) as a white foam, MH^+=640.

EXAMPLE 23

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-oxocyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-oxocyclohexyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.133g, 0.128mmol) was treated with trifluoroacetic acid (1.95ml) and water (0.5ml). The mixture was swirled until a solution had formed, and it was then left to stand at 21°C for 1.5h. The solution was evaporated and the residue was purified by preparative HPLC (30 to 70% acetonitrile) to give the title compound (0.088g) as a white foam, MH^+=600, nmr(δ,DMSO-d6) 1.00(t,3H), 1.80(m,2H), 2.20(m,2H), 2.35(m,4H), 3.15(m,2H), 4.60(m,4H), 5.90(d,1H), 7.15 to 7.40(m,10H), 8.25(m,3H).

EXAMPLE 24

(3S)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenyl thyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.4g) and (3S)-(+)-1-benzyl-3-aminopyrrolidine (1.23ml) was dissolved in dimethylsulphoxide (2ml) and heated and stirred at 140°C under nitrogen for 8h. The reaction was allowed to cool to 20°, then partitioned between ethyl acetate and water. The organic layer was washed with water, and the combined aqueous layers extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated to a residue which was purified on a column of silica eluting with ethyl acetate:methanol (50:1) to give the title compound (0.336g) as a white foam, nmr(δ,DMSO-d_6) 0.55(m,3H), 1.35(s,3H), 1.50(s,3H), 1.70(m,1H), 2.20(m,1H), 2.55 to 2.95(m,4H), 3.60(s,2H), 4.00 (m,2H), 4.40(m,2H), 4.55(m,1H), 5.40(m,2H), 6.15(s,1H), 6.45(m,1H), 7.10 to 7.35(m,17H), 7.75(s,1H).

Similarly prepared were:
(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide from the 2-chloropurine
(0.200g) and (+/-)-1-benzyl-3-aminopyrrolidine (0.614ml) in DMSO (1ml) at 140°C for 24h. The product was purified on silica eluting with ethyl acetate:methanol 50:1, MH^+=703.

1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-4-piperidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide from the 2-chloropurine (0.4g) and 1-benzyl-4-aminopiperidine (1.5g) at 135° for 24h. The product was purified on flash silica eluting with 1% methanol in ethyl acetate and dichloromethane:ethanol:0.880 ammonia (100:8:1), nmr(δ,$CDCl_3$) 0.7(t,3H), 1.35(s,3H), 1.4-1.65(m,2H), 1.6(s,3H), 1.95-2.3(m,4H), 2.8-3.1(m,4H), 3.5(s,2H), 3.7-3.95(m,1H), 4.1-4.3(m,2H), 4.34(t,1H), 4.65(s,1H), 4.77(d,1H), 5.4-5.6(m,3H), 5.97(s,2H), 7.15-7.35(m,15H), 7.4(s,1H).

EXAMPLE 25

(3R)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.4g) and (3R)-(-)-1-benzyl-3-aminopyrrolidine (1.23ml) was dissolved in dimethylsulphoxide (2ml) and heated and stirred at 140°C under nitrogen for 5h. The reaction was allowed to cool to 20°, then partitioned between ethyl acetate and water. The organic layer was washed with water, and the combined aqueous layers extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated to a residue which was purified on a column of silica eluting with ethyl acetate:methanol (50:1) to give the title compound (0.335g) as a white foam, nmr(δ,DMSO-d_6) 0.5(m,3H), 1.30(s,3H), 1.50(s,3H), 1.75 to 2.25(m,2H), 2.75(m,4H), 3.57(s,2H), 3.85 to 4.65(m,6H), 5.35(m,1H), 5.50(m,1H), 6.20(s,1H), 6.50(m,1H), 7.05 to 7.40(m,18H), 7.75(s,1H).

EXAMPLE 26

(3S)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of (3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.18g) in methanol (20ml) was added dropwise to a stirred suspension of 10% Palladium-on-carbon catalyst (0.027g) in methanol (10ml) under nitrogen . The mixture was treated with ammonium formate (0.08g) and the reaction mixture was stirred and heated at reflux for 2.5h. The cooled mixture was then filtered through Celite and the filtrate was evaporated to give a white foam which was purified by preparative HPLC (30 to 70% acetonitrile) to give the title compound as a white foam (0.166g), MH^+= 613.

Similarly prepared were:

(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide from (+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

under identical conditions. The filtered reaction mixture was evaporated to give the product directly, MH^+=613.

(3R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide from (3R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide under identical conditions, except that 0.070g of catalyst was used and the reaction time was 2h. The filtered reaction mixture was evaporated, and the residue purified by preparative HPLC (30 to 70% acetonitrile) to give the product, MH^+=613.

EXAMPLE 27

(3S)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

(3S)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.139g) was treated with trifluoroacetic acid (1.5ml) and water (0.4ml). The mixture was swirled until a solution had formed and it was then left to stand at 21°C for 1.5h. The reaction mixture was evaporated to a residue which was purified by preparative HPLC (20 to 60% acetonitrile) to give the title compound as a white foam (0.116g). Analysis found, C,47.4, H,4.5, F,17.1, N,12.15, H_2O,1.95%; $C_{30}H_{36}N_8O_4.2C_2F_3HO_2.H_2O$ requires C,47.0, H,4.5, F,17.5, N,12.3, H_2O,2.0%. nmr(δ,DMSO-d6) 1.00(t,3H), 1.95 to 2.30(m,2H), 3.05 to 3.50(m,6H), 4.05(m,2H), 4.20(m,1H), 4.25(s,1H), 4.60(m,4H), 5.85(d,1H), 6.95(m,1H), 7.15 to 7.40(m,10H), 7.65(m,1H), 8.15(m,2H), 8.80(m,2H).

Similarly prepared were:

(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from (+/-)-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-β-D-ribofuranuronamide (0.186g), trifluoracetic acid (2.6ml) and water (0.65ml) at 21°C for 1h. Purification by preparative HPLC (30 to 70% acetonitrile) gave the product, MH^+=573. nmr(δ,DMSO-d6) 1.00(t,3H), 2.10(m,2H), 3.25(m,6H), 4.00 to 4.20(m,3H), 4.25(s,1H), 4.55(m,3H),

5.85(d,1H), 6.95(m,1H), 7.15 to 7.40(m,10H), 7.65(m,1H), 8.10(m,1H), 8.20(s,1H), 8.80(m,2H).

(3R)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from (3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.112g), trifluoracetic acid (1.5ml) and water (0.4ml) at 21°C for 1.25h. Purification by preparative HPLC (20 to 60% acetonitrile) gave the product, MH^+=573. Analysis found, C,46.9, H,4.3, F,17.1, N,12.2; $C_{30}H_{36}N_8O_4.2C_2F_3HO_2.0.8H_2O$ requires C,47.3, H,4.5, F,17.4, N,12.45.

1-deoxy-N-ethyl-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-piperidinyl)amino]-9H-purin-9-yl]-β-D-ribofuranuronamide from 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-4-piperidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.15g) by hydrogenation in ethyl acetate over 10% palladium-in-carbon for 14 days then deprotection with trifluoroacetic acid (9ml) and water (1ml) at 21°C for 2.5h. Purification by preparative HPLC(20-60% acetonitrile) gave the product, MH^+=587, nmr(δ,DMSO-d6) includes 1.02(t,3H), 1.55-1.8(m,2H), 1.95-2.2(m,2H), 2.8-3.1(m,2H), 3.0-3.3(m,2H), 3.9-4.15(m,3H), 4.15-4.3(m,1H), 4.25(s,1H), 4.55(t,1H), 4.63(m,1H), 5.53(bm,1H), 5.83(d,1H), 7.1-7.4(m,10H), 8.05(s,1H), 8.0-8.2(m,1H), 8.2-8.4(m,1H), 8.4-8.6(m,1H).

EXAMPLE 28

(3R)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.4g) and (3R)-(-)-1-benzyl-3aminopyrrolidine (1.23ml) was dissolved in dimethylsulphoxide (2ml) and heated and stirred at 140°C under nitrogen for 5h. The reaction was allowed to cool to 20°, then partitioned between ethyl acetate and water. The organic layer was washed with water, and the combined aqueous layers extracted twice with ethyl acetate. The combined organic layers were washed

with brine, dried over sodium sulphate and vaporat d to a residue which was purified on a column of silica eluting with ethyl acetate:methanol (50:1) to give the title compound (0.335g) as a white foam, nmr(δ,DMSO-d_6) 0.5(m,3H), 1.30(s,3H), 1.50(s,3H), 1.75 to 2.25(m,2H), 2.75(m,4H), 3.57(s,2H), 3.85 to 4.65(m,6H), 5.35(m,1H), 5.50(m,1H), 6.20(s,1H), 6.50(m,1H), 7.05 to 7.40(m,18H), 7.75(s,1H).

EXAMPLE 29

(3R)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

(3R)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.125g) was treated with trifluoroacetic acid (1.5ml) and water (0.4ml). The mixture was swirled until a solution had formed then it was left to stand at 21°C for 1h. The reaction mixture was evaporated to give a residue which was purified by column chromatography on silica eluting with dichloromethane:methanol (9:1) to give the title compound (0.173g) as a white foam, MH+ 663; nmr(δ,DMSO-d6) 1.00(t.3H), 1.80 to 2.20(m,2H), 3.15(m,2H), 3.60(m,2H), 4.00(m,2H), 4.15(m,1H), 4.25(s,1H), 4.45(m,1H), 4.60(m,2H), 5.50(d,1H), 5.60(d,1H), 5.80(d,1H), 6.45(m,1H), 7.10 to 7.40(m,15H), 7.95(s,1H), 8.15(m,1H).

Similarly prepared were:

(+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from (+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.071g) with trifluoroacetic acid (0.5ml) and water (0.1ml) for 2.5h. The product was purified by preparative HPLC (30 to 70% acetonitrile),MH^+=663. Analysis found C,52.8, H,4.8, N,11.35, F,14.5%; $C_{37}H_{42}N_8O_4.2.5CF_3CO_2H.0.9H_2O$ requires C,52.4, H,4.85, N,11.6, F,14.8%.

(3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from (3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-

9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.125g) with trifluoroacetic acid (1.5ml) and water (0.4ml) for 1.5h. The product was purified by preparative HPLC (30 to 70% acetonitrile) to give 0.172g, MH^+=663. nmr(δ,DMSO-d6) 1.00(t.3H), 1.75(m,1H), 2.25(m,1H), 2.60 to 3.00(m,2H), 3.15(m,2H), 3.60(m,2H), 3.90 to 4.70(m,7H), 5.50(d,1H), 5.60(d,1H), 5.80(d,1H), 6.45(m,1H), 7.10 to 7.40(m,15H), 7.95(s,1H), 8.15(m,1H).

1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-4-piperidinyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-4-piperidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide(0.07g) in trifluoroacetic acid (9.5ml) and water (0.5ml) for 3h. The mixture was evaporated to dryness and the residue purified by reverse phase HPLC (20-60% acetonitrile). MH^+=677, nmr(δ,DMSO-d6) includes 1.0(t,3H), 1.55-1.8(m,2H), 1.85-2.15(m,1H), 2.05-2.3(m,2H), 2.8-3.15(m,1H),3.05-3.3(m,3H), 3.353.55(m,2H), 4.0-4.15(m,2H), 4.2(m,1H), 4.28(m,3H), 4.5(t,1H), 4.6(m,1H), 5.83(m;1H), 7.1-7.4(m,10H), 7.5(s,5H), 8.12(bs,2H).

EXAMPLE 30

(+/-)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(1-ethyl-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of (+/-)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.123g, 0.175mmol) in ethanol (analytical reagent grade) (10ml) was added slowly to a stirred suspension of 10% palladium-on-carbon catalyst (45mg) in ethanol (2ml). The mixture was then hydrogenated over 2.5days. The filtered solution was then evaporated and the residue was again hydrogenated in ethanol (12ml) over 10% palladium-on-carbon (40mg) for 2 weeks, but there was still no apparent reaction (tlc). The filtered mixture was evaporated and the residue was again hydrogenated over 10% palladium-in-carbon in ethanol at 250 p.s.i. pressure for 5days. The filtered mixture was evaporated and the residue was purified by preparative HPLC (30 to 70% acetonitrile) to give the title compound (0.068g) as a white foam, MH^+=641.

EXAMPLE 31

(+/-)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(1-ethyl-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

(+/-)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(1-ethyl-3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.060g) was treated with trifluoroacetic acid (0.5ml) and water (0.1ml), and the resulting solution was left to stand at 21°C for 1h. The solution was evaporated and the residue was purified by preparative HPLC (30 to 70% acetonitrile) to give the title compound (0.053g) as a white foam, MH^+=601, nmr(δ,DMSO-d6) 1.00(t,3H), 1.20(m,3H), 2.10(m,2H), 3.15(m,5H), 4.05(m,1H), 4.25(m,2H), 4.55(m,4H), 5.85(d,1H), 7.15 to 7.40(m,10H), 8.15(m,2H), 9.70(m,1H).

Prepared by a similar method to Examples 30 and 31 was:
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(1-ethyl-4-piperidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[1-(phenylmethyl)-4-piperidinyl]amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.14g) by hydrogenation in ethanol and deprotection with trifluoroacetic acid:water. The product was purified on reversed phase HPLC(20-60% acetonitrile). MH^+=587, nmr(δ,$CDCl_3$) includes 1.0(t,3H), 1.23(t,3H), 1.55-1.7(m,1H), 1.85-2.2(m,1H), 2.1-2.3(m,1H), 2.75-3.05(m,1H), 3.0-3.25(m,4H), 3.52(bd,1H), 4.25(s,1H), 4.53(t,1H), 4.6(m,1H), 5.85(d,1H), 7.15-7.4(m,10H), 8.13(bs,2H).

EXAMPLE 32

(trans)-1-[2-[(4-Aminocyclohexyl)amino]6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.4g) and trans-1,4-diaminocyclohexane (0.811g) was dissolved in dimethylsulphoxide (2.0ml) and heated and stirred at 140°C under nitrogen for 4h. The reaction mixture was allowed to cool to 21° and was then partitioned between (1:1) ethyl acetate and water (40ml). The organic layer was separated and washed with water. The combined aqueous layers were extracted twice with ethyl acetate, and the total organic solution was washed with brine, dried over sodium sulphate and evaporated in vacuo to a residue which was purified by preparative HPLC (30 to

70% acetonitrile) to give the title compound (0.342g) as a white foam , MH^+= 641.

Similarly prepared were:

1) 1-[2-[(3-aminopropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 1,3-diaminopropane as the nucleophile as in entry 1 in Table 3 below. The product had MH^+= 601.

2) 1-deoxy-[2-[(2,2-dimethyl-3-aminopropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using 2,2-dimethyl-1,3-propanediamine as the nucleophile as in entry 2 in Table 3 below. The product had MH^+= 629.

3) [(1α,2β,3β)-(+/-)]-1-[2-[(3-acetylamino-2-hydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide, using [(1α,2β,3β)-(+/-)]-3-acetylamino-2-hydroxycyclopentylamine[1] as the nucleophile as in entry 3 in Table 3 below, MH^+=685.

1. R.Vince and S.Daluge, J.Med.Chem., 1974, 17, 578

TABLE 3

Entry	2-chloropurine g.	nucleophile g.	DMSO ml	temp. °C	reaction time
1	0.30	0.395	1.5	140	1.5h
2	0.30	0.54	1.5	140	1.5h
3	0.20	0.25	0.8	140	18h

EXAMPLE 33

(trans)-1-[2-[(4-Aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

(trans)-1-[2-[(4-Aminocyclohexyl)amino]6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.277g) was treated with trifluoroacetic acid (2.0ml) and water(0.5ml). The

mixture was swirled until a solution had formed, then it was left to stand at 21°C for 2h. The reaction mixture was evaporated in vacuo to a residue which was purified by preparative HPLC (30 to 70% acetonitrile) to give the title compound (0.24g) as a white foam, MH^+=601; nmr(δ,DMSO-d6) 1.00(t,3H), 1.40(m,4H), 2.00(m,4H), 3.10(m,3H), 3.70(m,1H), 4.15(m,3H), 4.30(s,1H), 4.55(m,5H), 5.80(d,1H), 7.15 to 7.40(m,10H), 7.80(m,3H), 8.15(m,2H).

Similarly prepared were:

1) 1-[2-[(3-Aminopropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide, from the product from entry 1 in Table 3 above, as in entry 1 in Table 4 below. The product had MH^+=561, nmr(δ,DMSO-d6) includes 1.90(m,2H), 2.85(m,2H), 3.15(m,2H).

2) 1-deoxy-[2-[(2,2-dimethyl-3-aminopropyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the product from entry 2 in Table 3 above, as in entry 2 in Table 4 below. The product had MH^+=589, nmr(δ,DMSO-d6) includes 0.95(m,9H), 2.70(m,2H), 3.05 to 3.45(m,4H).

3) [(1α,2β,3β)-(+/-)]-1-[2-[(3-Acetylamino-2-hydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide from the product from entry 3 in Table 3 above, as in entry 3 in Table 4 below, MH^+=645; nmr(δ,DMSO-d6) includes 1.32 to 1.62(m,2H), 1.78 to 1.98(m,1H), 1.82(s,3H), 2.07 to 2.28(m,1H), 3.89(br.s,1H), 4.1(m,1H), 4.65(br.s,1H), 4.92(br.s,1H), 6.51(br.s,1H), 7.57(d,1H), the last three signals being exchangeable with D_2O.

TABLE 4

Entry	starting material g.	trifluoroacetic acid, ml	water ml	reaction time
1	0.2275	2.0	0.5	1.5h
2	0.2644	2.0	0.5	1.5h
3	0.098	1.0	0.1	2h

EXAMPLE 34

1-[2-(Cyclopentylamino)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (0.407g, 0.78mmol) and cyclopentylamine (6ml) was stirred and refluxed under nitrogen for 26h. Sodium hydrogen carbonate (0.600g) was added and the mixture was stirred at 21°C for 0.5h. The mixture was evaporated and purified on flash silica eluting with dichloromethane:ethanol:0.880 ammonia (75:8:1) to give an impure product which was purified on flash silica eluting with 2 to 5% methanol in ethyl acetate to give a product which was triturated with ether to give the title compound (0.205g) as a white solid, m.p. 122 to 128°C. Found C,64.8, H,6.7, N,17.0%. $C_{51}H_{37}N_7O_4$ requires C,65.1, H,6.5, N, 17.15%.

Similarly prepared was:

(1R-trans)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide, from the 2-chloropurine (0.35g) and (R)-(trans)-2-aminocyclopentanol[1] (1.0g) at 130°C for 10h. The product was purified on silica eluting with ethyl acetate:methanol 19:1 and then on silica eluting with dichloromethane:methanol:0.880 ammonia (100:8:1). The product had m.p. 122 to 130°C. Analysis found C,62.6, H,6.2, N,16.2%; $C_{31}H_{37}N_7O_5.0.4H_2O$ requires C,62.6, H,6.4, N,16.5%.

1. L.E.Overman and S.Sugai, J.Org.Chem., 1985, 50, 4154

EXAMPLE 35

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(2-hydroxyphenyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (0.20g, 0.38mmol), 2-aminophenol (0.20g, 1.83mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.052ml, DBU) and dimethylsulphoxide (1ml) was stirred and heated at 140°C under nitrogen for 6h, and then left at 21°C overnight. The mixture was partitioned between ethyl acetate (200ml) and water (40ml). The aqueous layer was extracted with more ethyl acetate (50ml) and the total organic solution was washed (water, 20ml), dried (Na_2SO_4) and evaporated. The residue was purified on flash silica eluting

with dichloromethane:methanol (19:1), and then by preparative TLC (20 x 20cm plate with 2mm layer of Kieselgel 60 F_{254}; Art 5717) in dichloromethane:ethyl acetate:ethanol 9:9:2, and then by preparative HPLC (30 to 70% acetonitrile) to give the title compound (0.018g) as a cream foam, MH^+= 596. Analysis found: C,52.2, H,4.3, N,11.8; $C_{32}H_{33}N_7O_5.2CF_3CO_2H$ requires C,52.5, H,4.3, N,11.9%.

Similarly prepared was:
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(4-hydroxyphenyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide from the 2-chloropurine (0.135g), 4-aminophenol (0.135g), DBU (0.035ml) and DMSO (0.6ml) at 140°C for 10h.The product was extracted into dichloromethane, and purification was by preparative TLC and preparative HPLC (same system as above). The product had MH^+= 596 and nmr(δ,DMSO-d6) including 7.09(d,2H) and 7.27(d,2H).

EXAMPLE 36

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide hydrochloride salt

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (0.155g,0.296mmol) and histamine (0.22g) in dimethylsulphoxide (1.5ml) was heated at 120°C for 16h. The mixture was cooled and diluted with ethyl acetate (50ml) then washed with water (50ml). The aqueous phase was extracted with ethyl acetate (50ml) and the combined organic phase was washed with water (50ml), dried ($MgSO_4$) and evaporated to leave a solid which was treated with 2N hydrochloric acid (2ml) in methanol (30ml) and the solution was evaporated to leave the title compound (0.15g,80%) as a solid. MH^+=598, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.0(m,2H), 3.13(m,2H), 3.7(m,2H), 4.2(m,2H), 4.85(s,1H), 4.55(m,3H), 5.9(d,1H), 7.1-7.6(m,12H), 8.45(s,1H), 9.05(s,1H), 14.3(m,1H).

EXAMPLE 37

N-[6-[(2,2-Diphenylethyl)amino]-9-[N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]-L-phenylalanine, 1,1-dimethylethyl ester and

N-[6-[(2,2-diphenylethyl)amino]-9-[N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]-D-phenylalanine, 1,1-dimethylethyl ester

A mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.402g,0.714mmol) and L-phenylalanine 1,1-dimethylethyl ester (0.3g) was heated at 130°C for 17h when more amine (0.4g) was added. Heating was continued for a further 29h then more amine (0.37g then 0.4g after 3h) was added and the reaction left for a further 74h at 130°C. The cooled residue was purified by flash chromatography using 70% ethyl acetate in cyclohexane and preparative HPLC (70-100% acetonitrile) and the resultant solution brought to pH 8 with sodium hydrogen carbonate. The mixture was reduced in volume and the product was extracted with ethyl acetate(3x75ml) in the presence of salt solution. The extract was dried and evaporated to give the mixture of title compounds (0.2g) as a solid, MH^+=748.

EXAMPLE 38

N-[6-[(2,2-Diphenylethyl)amino]-9-(N-ethyl-β-D-ribofuranuronamidosyl)-9H-purin-2-yl]-L-phenylalanine and

N-[6-[(2,2-diphenylethyl)amino]-9-(N-ethyl-β-D-ribofuranuronamidosyl)-9H-purin-2-yl]-D-phenylalanine

A solution of N-[6-[(2,2-diphenylethyl)amino]-9-[N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]-L-phenylalanine, 1,1-dimethylethyl ester and N-[6-[(2,2-diphenylethyl)amino]-9-[N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamidosyl]-9H-purin-2-yl]-D-phenylalanine, 1,1-dimethylethyl ester (0.152g,0.203mmol) in 9:1 trifluoroacetic acid:water (5ml) was kept at room temperature for 3.5h then evaporated to give a solid which was purified by preparative HPLC (48% acetonitrile isocratic).

Isomer 1 (0.019g,14%) had MH^+=652, nmr(δ,DMSO-d6) includes 0.98(t,3H), 3.0-3.2(m,4H), 4.0-4.15(m,3H), 4.27(bs,1H), 4.5-4.65(m,2H), 4.7-4.8(m,1H), 5.81(bd,1H), 7.1-7.4(m,15H), 8.05-8.15(bs,1H).

Isomer 2 (0.0466g,35%) had MH^+= 652, nmr(δ,DMSO-d6) includes 0.8-0.95(m,3H), 3.0-3.2(m,4H), 4.0-4.15(m,3H), 4.25(bs,1H), 4.55-4.7(m,2H), 4.7-4.8(m,1H), 5.8(bd,1H), 7.1-7.4(m,15H), 8.05-8.15(bs,1H).

EXAMPLE 39

(trans)-1-[2-[(4-Aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (18.0g,0.0344mole) in dimethylsulphoxide (100ml) was heated at 120° under nitrogen with trans-cyclohexane-1,4-diamine (29.5g, 0.258mole) for 48h. The cooled mixture was diluted with ethyl acetate (1l) and water (500ml). The aqueous phase, which contained a considerable amount of oil, was separated from the ethyl acetate. The water was decanted from the oil and then extracted with ethyl acetate (100ml) and the ethyl acetate solutions were combined, dried (MgSO4) and evaporated to leave a froth (9.2g). The oil was dissolved in ethanol (500ml) and the solution was evaporated to leave a solid which was dried in vacuo. The solid was leached with ethanol (3x200ml) and the filtered solution was evaporated in vacuo to leave a froth (11.1g). The two product fractions were combined and purified by column chromatography on flash silica eluted with dichloromethane:ethanol:0.88 ammonia (30:8:1) to give the title compound (17.11g). The product had nmr(δ,$CDCl_3$) including 1.1(t,3H), 1.1-1.35(m,4H),1.75-1.95(m,2H), 1.95-2.2(m,2H), 3.05-3.25(m,1H), 3.2-3.5(m,1H), 4.5-4.8(m,1H), 4.1-4.3(m,2H), 4.35(t,1H), 4.5(d,1H), 4.67(d,1H), 4.8(m,2H), 5.7-5.9(m,1H), 5.8(d,1H), 7.1-7.4(m,10H), 7.47(s,1H).

EXAMPLE 40

(trans)-1-[2-[(4-Aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide hydrochloride

A solution of (trans)-1-[2-[(4-Aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (11.05g, 0.0184mole) in ethanol (120ml) was stirred during the addition of 1M hydrogen chloride in ether (18.4ml, 0.0184mole). An initial precipitate redissolved on complete addition and the mixture was stirred for 15 min before ether (400ml) was added. The resulting precipitate was stirred for a further 15 min then collected by filtration under nitrogen and dried in vacuo at 60° over phosphorus pentoxide. The solid (10.1g) was crystallised from isopropanol (120ml) to give the title compound (7.95g). The product had MH^+=601, nmr(δ,DMSO-d6) includes 1.0(t,3H), 1.2-1.5(m,4H), 1.9-2.1(m,4H), 2.9-3.1(m,1H), 3.0-3.3(m,2H), 3.6-3.8(m,1H), 3.9-4.2(m,2H), 4.1-4.2(m,1H),

4.25(s,1H), 4.5-4.6(m,1H), 4.6-4.7(m,1H), 5.4-5.7(m,2H), 5.8(d,1H), 6.2-6.4(m,1H), 7.1-7.4(m,10H), 7.95(bs,1H), 7.8-8.2(m,3H).

EXAMPLE 41

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino]-N-ethyl-9H-purin-9-yl]-β-D-ribofuranuronamide

A solution of sodium hydroxide (242mg, 6.05mmol) in methanol (20ml) was added to a suspension of 1-methylhistamine dihydrochloride (600mg, 3.029mmol) in methanol (10ml). The mixture was stirred for 0.5h to give a fine precipitate. The mixture was blown dry with nitrogen. A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (253mg, 0.484mmol) in dimethylsulphoxide (2ml) was added and the mixture was heated at 125° for 24h under nitrogen. The cooled mixture was partitioned between ethyl acetate (50ml) and water (20ml). The aqueous phase was extracted with ethyl acetate (20ml) and the combined organic phase was washed with water (50ml), dried (MgSO4) and evaporated to leave a solid which was purified by preparative HPLC (30-70% acetonitrile) to give the title compound (251mg). The product had MH^+=612, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.95-3.05(m,2H), 3.05-3.25(m,2H), 3.5-3.85(m,2H), 3.8(s,3H), 4.38(s,1H), 4.5-4.65(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 7.45(s,1H), 8.13(s,1H), 8.1-8.3(m,1H), 8.95(s,1H).

Similarly prepared were:

1) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(3-methyl-3H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 3-methylhistamine (prepared by basification of the dihydrochloride) as the nucleophile as in entry 1 in Table 5 below. The product was purified by preparative HPLC (30 to 70% acetonitrile). The product had MH^+=612, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.85-3.05(m,2H), 3.05-3.25(m,2H), 3.55-3.85(m,2H), 3.78(s,3H), 3.95-4.15(m,2H), 4.18 and 4.3 (bs,3H), 4.45-4.65(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 7.48(s,1H), 8.1-8.3(m,2H), 9.0(s,1H).

2) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-imidazol-2-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 2- (1H-imidazol-2-

yl)ethylamine[1] (prepared by basification of the dihydrochloride) as the nucleophile as in entry 2 in Table 5 below. The product was purified by preparative HPLC (25 to 56% acetonitrile over 14 min. then to 90% at 16 min.). The product had MH^+= 598, nmr(δ,DMSO-d6) includes 0.91(t,3H), 3.90-4.05(m,2H), 4.10-4.16(m,1H), 4.45-4.55(m,2H), 5.77(d,1H), 7.10-7.30(m,12H), 7.40-7.50(m,2H), 8.00-8.10(m,2H).

1. Durant, G. J. et al, Chem. Comm., 1968, (2), 108-110.

3) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[(1H-imidazol-4-yl)methyl]amino]-9H-purin-9-yl]N-ethyl-β-D-ribofuranuronamide using (1H-imidazol-4-yl)methylamine[1] (prepared by basification of the dihydrochloride) as the nucleophile as in entry 3 in Table 5 below. The product was purified by preparative HPLC (25 to 56% acetonitrile over 14 min. then to 90% at 16 min.). The product had MH^+= 584, nmr(δ,DMSO-d6) includes 1.07(t,3H), 3.10-3.30(m,2H), 4.00-4.10(m,2H), 4.22-4.27(m,1H), 4.34(bs,1H), 4.50-4.70(m,4H), 5.92(d,1H), 7.20-7.40(m,14H), 7.51(s,1H), 8.20(bs,1H), 9.05(bs,1H).

1. Turner, R. A., Huebner, C. F. and Scholz, C. R., J. Am. Chem. Soc., 1949, 71, 2801-2803.

4) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[3-(1H-imidazol-4-yl)propyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 3-(1H-imidazol-4-yl)propylamine[1] (prepared by basification of the dihydrochloride) as the nucleophile as in entry 4 in Table 5 below. The product was purified by preparative HPLC (25 to 56% acetonitrile over 14 min. then to 90% at 16 min.). The product had MH^+= 612, nmr(δ,DMSO-d6) includes 1.01(t,3H), 1.90-2.00(m,2H), 2.70(bt,4H), 3.10-3.25(m,2H), 4.00-4.10(m,2H), 4.15-4.24(m,1H), 4.30(s,1H), 4.55-4.65(m,4H), 5.84(d,1H), 7.15-7.35(m,10H), 7.42(s,1H), 8.12(s,1H), 8.15-8.25(m,1H), 8.98(s,1H).

1. Adger, B. M. and Surtees, J., Synth. Comm., 1987, 17(2), 223-227.

5) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[(1H-imidazol-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 2-(1H-imidazol-1-yl)ethylamine[1] (prepared by basification of the dihydrobromide) as the nucleophile as in entry 5 in Table 5 below. The product was purified by preparative HPLC (27 to 54% acetonitrile over 14.5 min.). The product had

MH^+= 598, nmr(δ,DMSO-d6) includes 0.98(t,3H), 3.05-3.20(m,2H), 4.00-4.10(2H), 4.15-4.25(m,1H), 4.27(bs,1H), 4.38-4.48(m,2H), 4.50-4.62(m,2H), 5.83(d,1H), 6.74-6.85(m,1H), 7.15-7.40(10H), 7.60-7.70(m,2H), 7.72(s,1H), 8.10-8.20(m,2H), 9.05(bs,1H).

1. Cuadro, A. M. et al., Synth. Comm., 1991, 21(4), 535-544.

6) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(pyrid-3-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 3-(2-aminoethyl)pyridine[1] as the nucleophile as in entry 6 in Table 5 below. The product was purified by preparative HPLC (20 to 60% acetonitrile). The product had MH^+= 609, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.95-3.25(m,4H), 3.55-3.8(m,2H), 5.87(d,1H), 7.15-7.4(m,10H), 7.8(dd,1H), 8.0-8.5(m,3H), 8.65-8.8(m,2H).

1. Soeda, Y. and Yamamoto, I., Agr. Biol. Chem. (Tokyo), 1968, 32(6), 747-752.

7) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(pyrid-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 4-(2-aminoethyl)pyridine[1] as the nucleophile as in entry 7 in Table 5 below. The product was purified by preparative HPLC (25 to 47.5% acetonitrile). The product had MH^+= 609, nmr(δ,DMSO-d6) includes 1.09(t,3H), 3.00-3.22(m,4H), 4.00-4.10(m,2H), 4.15-4.21(m,1H), 4.30(bs,1H), 4.52-4.62(m,2H), 5.83(d,1H), 7.15-7.35(m,10H), 7.81(d,2H), 8.10-8.25(m,2H), 8.71(d,2H).

1. Magnus, G. and Levine, R., J. Am. Chem. Soc., 1956, 78, 4127-4130.

8) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[(pyrid-3-yl)methyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 3-aminomethylpyridine as the nucleophile as in entry 8 in Table 5 below. The product was purified by preparative HPLC (25 to 56% acetonitrile over 14 min. then to 90% at 16 min.). The product had MH^+= 595, nmr(δ,DMSO-d6) includes 1.01(t,3H), 3.10-3.25(m,2H), 4.29(d,1H), 4.40-4.56(m,3H), 4.65-4.72(bs,2H), 5.83(d,1H), 7.10-7.30(m,10H), 7.75-7.81(m,2H), 8.13-8.30(m,3H), 8.68(d,1H), 8.75(bs,1H).

9) 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-1,2,4-triazol-3-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 3-(2-aminoethyl)-1,2,4-triazole[1] (prepared by basification of the dihydrochloride) as

the nucleophile as in entry 9 in Table 5 below. The product was purified by preparative HPLC (20 to 65% acetonitrile). The product had MH^+= 599, nmr(δ,DMSO-d6) includes 1.01(t,3H), 3.00-3.20(m,4H), 4.35(d,1H),4.50-4.65(m,3H), 5.87(d,1H), 7.10-7.40(m,10H), 8.20-8.50(m,3H).

1. Ainsworth, C. and Jones, R., J. Am. Chem. Soc., 1953, 75, 4915-4918.

10)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1H-1,2,4-triazol-1-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 1-(2-aminoethyl)-1,2,4-triazole[1] (prepared by basification of the dihydrobromide) as the nucleophile as in entry 10 in Table 5 below. The product was purified by preparative HPLC (29 to 51% acetonitrile). The product had MH^+= 599, nmr(δ,DMSO-d6) includes 1.00(t,3H), 3.10-3.20(m,2H), 5.85(d,1H), 6.80-6.95(m,1H), 7.10-7.40(m,10H), 8.00(bs,1H), 8.16(m,2H), 8.47(bs,1H).

1. Cuadro, A. M. et al., Synth. Comm., 1991, 21(4), 535-544.

11)1-deoxy-1-[2-[[(5-amino-1H-tetrazol-1-yl)ethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 1-(2-aminoethyl)-5-amino-1H-tetrazole (prepared by basification of the dihydrobromide) as the nucleophile as in entry 11 in Table 5 below. The product was purified by preparative HPLC (40 to 60% acetonitrile). The product had MH^+= 615, nmr(δ,DMSO-d6) includes 1.03(t,3H), 3.05-3.25(m,2H), 4.0-4.3(m,2H), 4.38(bs,1H), 4.45-4.6(m,1H), 4.55-4.75(m,2H), 5.87(d,1H), 7.1-7.4(m,10H), 8.3(bs,1H).

12)(trans)-1-deoxy-1-[2-[(4-N,N-dimethylaminocyclohexyl)amino]6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 4-(N,N-dimethylamino)cyclohexylamine as the nucleophile as in entry 12 in Table 5 below. The product was purified by column chromatography on silica eluted with dichloromethane:ethanol:0.88 ammonia (30:8:1) then preparative HPLC (30 to 70% acetonitrile). The product had MH^+= 629, nmr(δ,DMSO-d6) includes 1.0(t,3H), 1.2-1.6(m,4H), 1.95-2.25(m,4H), 2.75(s,6H), 3.05-3.3(m,3H), 3.6-3.85(m,1H), 4.0-4.15(m,2H), 4.15-4.25(m,1H), 4.3(s,1H), 4.4-4.75(m,2H), 5.85(d,1H), 7.15-7.45(m,10H), 8.2(bs,1H), 9.5(m,1H).

13)1-deoxy-1-[2-[[(4-amino-pyrimidin-5-yl)methyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 4-amino-5-aminomethyl-pyrimidine[1] as the nucleophile as in entry 13 in Table 5 below. The product was purified by column chromatography on silica eluted with dichloromethane:ethanol:0.88 ammonia (30:8:1) then preparative HPLC (20 to 60% acetonitrile). The product had MH^+= 611, nmr(δ,DMSO-d6) includes 1.0(t,3H), 3.05-3.25(m,2H), 4.17(m,1H), 4.3(s,1H), 4.35-4.45(m,1H), 4.45-4.6(m,2H), 5.85(d,1H), 7.0-7.4(m,10H), 8.05-8.2(3H), 8.7(s,1H).

1. Neef, H., Kohnert, K. D., Schellenberger, A., J. Prakt. Chem., 1973, 315(4), 701.

14)1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-methyl-1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide using 2-(2-methyl-1H-imidazol-4-yl)ethylamine[1] as the nucleophile as in entry 14 in Table 5 below. The product was purified by preparative HPLC (25 to 46% acetonitrile over 11.5 min.). The product had MH^+= 612, nmr(δ,DMSO-d6) includes 1.0(t,3H), 2.85-3.0(m,2H), 3.1-3.25(m,2H), 3.5-3.7(m,2H), 4.0-4.15(m,2H), 4.15-4.25(m,1H), 4.3(s,1H), 5.82(d,1H), 6.8-7.05(m,1H), 7.1-7.4(m,10H), 7.8-8.0(m,1H), 8.1-8.3(m,2H), 13.7-13.8(bs,1H), 13.85-14.0(bs,1H).

1. Dziuron, P. and Schunack, W. Eur. J. Med. Chem.-Chimica Therapeutica, 1975, 10(2) 129.

TABLE 5

Entry	2-chloropurine g.	nucleophile g.	DMSO ml	temp. °C	reaction time
1	0.253	0.6 (HCl salt)	2.0	130	24h
2	0.250	0.439(HCl salt)	1.0	130	20h
3	0.203	0.45(HCl salt)	1.5	130	25h
4	0.117	0.230(HCl salt)	1.0	120	24h
5	0.250	0.655(HBr salt)	0.5	130	19h
6	0.254	0.3	2.0	120	24h
7	0.250	0.292	1.0	130	22h
8	0.200	0.154 ml	1.0	125	20h
9	0.200	0.318(HCl salt)	1.0	130	20h
10	0.250	0.655(HBr salt)	0.5	130	42h

11	0.171	0.209	0.7	120	24h
12	0.368	0.5	1.5	145	16h
13	0.275	1.0	2.0	120	20h
14	0.350	0.42	1.5	130	16.5h

EXAMPLE 42

1-Deoxy-1-[2-[[2-[(aminoiminomethyl)amino]ethyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (0.382g, 0.73mmol) in dimethylsulphoxide (2.5ml) was heated at 125° for 18h with ethylenediamine (1.15g, 19.2mmol) under nitrogen. The cooled mixture was partitioned between ethyl acetate (50ml) and water (50 ml) and the aqueous phase was separated, extracted with ethyl acetate (20ml) and the extract was combined with the organic phase from the partitioning. The organic solution was dried ($MgSO_4$) and evaporated to leave a brown froth (0.373g). This froth (0.353g) was dissolved in 50% aqueous methanol (20ml) and the solution was heated at 50° with pyrazole-1-carboxamidine hydrochloride (0.099g, 0.675mmol) for 18h. More pyrazole-1-carboxamidine hydrochloride (0.099g, 0.675mmol) and imidazole (0.048g, 0.705mmol) were added and the reaction was heated at 50° for a further 18h. The mixture was evaporated to leave a red oil which was purified by preparative HPLC (20-60% acetonitrile) to give the title compound (0.23g) as a solid from ether. The product had MH^+=589, nmr(δ,DMSO-d6) includes 1.02(t,3H), 3.05-3.25(m,2H) 3.3-3.5(m,2H), 3.4-3.6(m,1H), 4.8(s,1H), 4.5-4.7(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 7.57(m,1H), 8.12(s,1H), 8.1-8.25(m,1H).

EXAMPLE 43

1-Deoxy-1-[2-[[3-[(aminoiminomethyl)amino]propyl]amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (0.310, 0.592mmol) in dimethylsulphoxide (2ml) was heated with 1,3-diaminopropane (0.542g, 7.31mmol) at 120° for 24h. The cooled mixture was partitioned between ethyl acetate (50ml) and water (50ml) and the aqueous phase was separated and extracted with ethyl acetate (20ml). The combined ethyl acetate solution was washed with water (20ml), dried

($MgSO_4$) and vaporated to leave a froth (0.302g). This froth (0.3g)was dissolved in 50% aqueous methanol (20ml) and the solution was heated at reflux with pyrazole-1-carboxamidine hydrochloride (0.099g, 0.675mmol) and imidazole (0.05g, 0.734mmol) for 18h. More pyrazole-1-carboxamidine hydrochloride (0.099g, 0.675mmol) was added and heating was continued for a further 24h. The mixture was evaporated to leave a solid which was purified by preparative HPLC (20-60% acetonitrile) to give the title compound (0.202g) as a solid from ether. The product had MH^+= 603, nmr(δ,DMSO-d6) includes 1.02(t,3H), 1.7-1.9(m,2H), 3.05-3.25(m,4H), 3.3-3.5(m,2H), 4.15-4.25(m,1H), 4.8(s,1H), 4.5-4.7(m,2H), 5.85(d,1H), 7.15-7.4(m,10H), 7.5-7.65(m,1H), 8.12(s,1H), 8.1-8.25(m,1H).

EXAMPLE 44

The effects of compounds of the invention on fMLP activation of O_2^- generation

The potential for compounds of formula (I) to inhibit leukocyte function was examined by measuring the ability of the compounds to inhibit superoxide (O_2^-) generation from neutrophils stimulated with fMLP following the procedure described by W. Busse et al. in J. Allergy Clin. Immunology, 83(2) Part 1, 400-405 (1989). In this test the deprotected compounds of the specific examples were shown to inhibit O_2^- generation. Thus, for example, compounds of Examples 2, 5, 7, 10, 12, 14, 15, 19, 21, 21(3), 21(4), 21(5), 21(6), 21(7), 21(8), 21(11), 21(12), 21(13), 21(14), 21(15), 21(16), 21(21), 21(22), 21(23), 21(25), 21(26), 21(31), 21(36), 21(37), 27, 27(2), 29, 31, 31(1), 33, 33(3), 34(1), 41, 41(2), 41(4), 41(9), 41(12), 41(14), 42 and 43 were at least as active as NECA in this study. Indeed, the compound of Example 33 is 25 times more potent than NECA in this study.

Antigen-induced lung eosinophil accumulation in sensitised guinea pigs

Ovalbumin-sensitised guinea pigs were dosed with mepyramine (1mg/kg ip) to protect against anaphylactic bronchospasm. A compound of the invention was then given ip 30 minutes before ovalbumin challenge (30 minutes breathing of an aerosol generated from a 50μg/ml solution of ovalbumin). A second dose of test compound was administered 6 hours after the first dose. Twenty-four hours after challenge, the guinea pigs were killed and bronchoalveolar lavage performed. Total and differential cell counts were then made and the dose of

test compound giving a 50% reduction of cell accumulation (ED_{50}) was calculated.

Results

In the above test, the compound of Example 33 has an average ED_{50} of 10μg/kg.

Administration of the compound of Example 33 to guinea pigs ip produced no visible toxic effects at single doses up to 100μg/kg.

The following are examples of suitable formulations of compounds of the invention. The term "active ingredient" is used herein to represent a compound of the invention and can be, for example, the compound of Example 33.

1. Injection for Intravenous Administration

		mg/ml
Active ingredient		0.5mg
Sodium Chloride BP		as required
Water for Injection BP	to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

2. Inhalation Cartridges

		mg/cartridge
Active ingredient micronised		0.200
Lactose BP	to	25.0

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

3. Metered Dose Pressurised Aerosol

A. Suspension Aerosol

	mg/metered dose	per can
Active ingredient micronised	0.100	26.40mg
Oleic Acid BP	0.010	2.64mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10 - 15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension, are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

B. Solution Aerosol

	mg/metered dose	per can
Active ingredient	0.100	24.0mg
Ethanol BP	7.500	1.80mg
Trichlorofluoromethane BP	18.875	4.53g
Dichlorodifluoromethane BP	48.525	11.65g

Oleic acid BP, or a suitable surfactant, e.g. Span 85 (sorbitan trioleate) may also be included.

The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

C. Alternative Suspension Aerosol

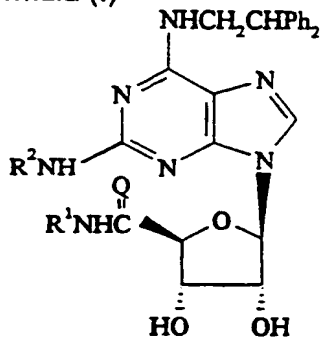
	mg/metered dose	per can
Active ingredient	0.100	24.0mg
1,1,1,2-tetrafluoroethane	75.0	18.0g

Oleic acid BP or a suitable surfactant may also be included.

The active ingredient is dispersed in the propellant held as a liquid at high pressure and/or low temperature. The resulting dispersion is then metered into suitable containers either at low temperatures prior to crimping a metering valve or by pressure filling through a pre-crimped metering valve.

CLAIMS

1. A compound of formula (I)



(I)

and salts and solvates thereof, wherein:

R^1 represents a hydrogen atom or a C_{3-8}cycloalkyl or C_{1-6}alkyl group;

R^2 represents a group selected from

(i) C_{3-8}cycloalkyl

(ii) C_{3-8}cycloalkyl substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p is zero or 1 and R^3 is hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino)

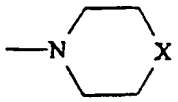
(iii) pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl)

(iv) pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl) and one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(v) C_{3-8}cycloalkylC_{1-6}alkyl

(vi) C_{3-8}cycloalkylC_{1-6}alkyl in which one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(vii) -Alk_1Y where Alk_1 is a C_{2-6} alkyl ne group and Y is a group selected from C_{2-7}acylamino, guanidino, hydroxyl, NH_2, C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O, CH_2 or NR^4 in which R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl) and

(viii) -$(CHR^5)_m(Alk_2)_nZ$ where m and n each independently represent zero or 1 except that when m is 1 then n must also represent 1, R^5 is a hydrogen atom or a carboxy group or a group CH_2R^6 (where R^6 is C_{2-7}acylamino, guanidino, hydroxy, methoxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino), Alk_2 is a C_{1-5}alkylidene group and Z is a hydrogen atom or an optionally substituted aromatic ring selected from phenyl, pyridyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl and benzimidazolyl where the ring is optionally substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{1-6}alkyl, C_{2-7}acylamino, guanidino, carboxyethyl, hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino;

Q represents an oxygen or sulphur atom; and

Ph represents phenyl.

2. A compound according to Claim 1 in which R^1 is C_{1-3} alkyl.

3. A compound according to Claim 1 or Claim 2 in which Q is an oxygen atom.

4. A compound according to Claim 1 in which $R^1NHC(=Q)$- is ethylaminocarbonyl.

5. A compound according to any preceding claim in which R^2 is cyclopentyl or cyclohexyl each substituted by one or two groups selected from C_{2-7} acylamino, guanidino, carboxyl, oxo and $(CH_2)_pR^3$.

6. A compound according to Claim 5 in which R^2 is cyclopentyl or cyclohexyl each substituted by one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino, acetamido or trifluoroacetamido.

7. A compound according to any of Claims 1 - 4 in which R^2 is pyrrolidin-3-yl or piperidin-3-yl in which the respective rings may each be substituted by hydrogen, C_{1-3} alkyl or benzyl.

8. A compound according to any of Claims 1 - 4 in which R^2 is $-(CHR^5)m(Alk_2)_nZ$ in which Z is an optionally substituted imidazolyl group.

9. A compound according to Claim 8 in which $-(CHR^5)m(Alk_2)_n-$ is $-CH_2CH_2-$.

10. (1S-trans)-1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-hydroxycyclopentyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[1S-(1α,2β,3β)]-1-deoxy-1-[2-[(2,3-dihydroxycyclopentyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
[(1S)-trans]-1-deoxy-1-[2-[(3-N,N-dimethylamino)cyclopentylamino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(3S)-1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[(3-pyrrolidinyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
(trans)-1-[2-[(4-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino]-N-ethyl-9H-purin-9-yl]-β-D-ribofuranuronamide;
(trans)-1-deoxy-1-[2-[(4-N,N-dimethylaminocyclohexyl)amino]6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(2-methyl-1H-imidazol-4-yl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
and physiologically acceptable salts and solvates thereof.

11. (trans)-1-[2-[(4-Aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide; and physiologically acceptable salts and solvates thereof.

12. The hydrochloride salt of (trans)-1-[2-[(4-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide.

13. A compound of formula (I) as defined in Claim 1 with the proviso that Z cannot represent an optionally substituted triazolyl or tetrazolyl ring.

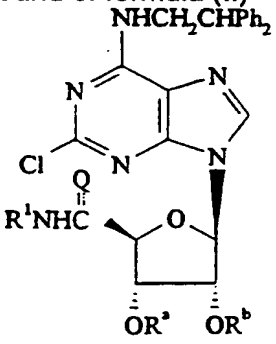
14. A compound of formula (I) as defined in any preceding claim for use in human or veterinary medicine.

15. Use of a compound of formula (I) as defined in any preceding claim for the manufacture of a medicament for the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

16. A pharmaceutical composition comprising a compound of formula (I) as defined in any preceding claim together, if desirable, with one or more physiologically acceptable carriers or excipients.

17. A process for the preparation of a compound of formula (I) as defined in Claim 1, which comprises:

(A) treating a compound of formula (II)



(II)

(wh rein R^a and R^b are each hydrogen or together form an alkylidene group) with an amine $R^{2a}NH_2$ (wherein R^{2a} is a group R^2 or a protected derivative thereof), followed, where necessary, by the removal of any protecting groups present; or

(B) deprotecting a protected derivative of a compound of formula (I),

if necessary or desirable followed by (i) salt formation or (ii) conversion of a compound of formula (I) to a different compound of formula (I) or (iii) preparation of an individual isomer of a compound of formula (I).

18. A method for the treatment of a human or animal subject with an inflammatory condition which is susceptible to leukocyte-induced tissue damage, which method comprises administering to said subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

19. Compounds according to any of Claims 1 to 12 substantially as herein described.

20. Compositions according to Claim 16 substantially as herein described.

21. A process for the preparation of a compound according to Claim 1, the process substantially as herein described and exemplified.

AMENDED CLAIMS

[received by the International Bureau on 20 May 1994 (20.05.94);
original claims 1-12 unchanged; new claim 13 added;
original claims 13-21 renumbered as 14-22(2 pages)]

11. (trans)-1-[2-[(4-Aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide; and physiologically acceptable salts and solvates thereof.

12. The hydrochloride salt of (trans)-1-[2-[(4-aminocyclohexyl)amino]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide.

13. 1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[[2-(1-piperidinyl)ethyl]amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
and physiologically acceptable salts and solvates thereof.

14. A compound of formula (I) as defined in Claim 1 with the proviso that Z cannot represent an optionally substituted triazolyl or tetrazolyl ring.

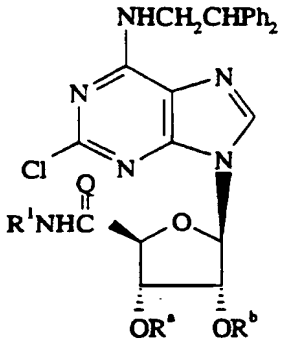
15. A compound of formula (I) as defined in any preceding claim for use in human or veterinary medicine.

16. Use of a compound of formula (I) as defined in any preceding claim for the manufacture of a medicament for the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

17. A pharmaceutical composition comprising a compound of formula (I) as defined in any preceding claim together, if desirable, with one or more physiologically acceptable carriers or excipients.

18. A process for the preparation of a compound of formula (I) as defined in Claim 1, which comprises:

(A) treating a compound of formula (II)



(II)

(wherein R^a and R^b are each hydrogen or together form an alkylidene group) with an amine $R^{2a}NH_2$ (wherein R^{2a} is a group R^2 or a protected derivative thereof), followed, where necessary, by the removal of any protecting groups present; or

(B) deprotecting a protected derivative of a compound of formula (I),

if necessary or desirable followed by (i) salt formation or (ii) conversion of a compound of formula (I) to a different compound of formula (I) or (iii) preparation of an individual isomer of a compound of formula (I).

19. A method for the treatment of a human or animal subject with an inflammatory condition which is susceptible to leukocyte-induced tissue damage, which method comprises administering to said subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

20. Compounds according to any of Claims 1 to 13 substantially as herein described.

21. Compositions according to Claim 17 substantially as herein described.

22. A process for the preparation of a compound according to Claim 1, the process substantially as herein described and exemplified.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/00145

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07H19/167 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 277 917 (CIBA-GEIGY AG) 10 August 1988 see the whole document ---	1-21
Y	EP,A,0 222 330 (WARNER-LAMBERT COMPANY) 20 May 1987 see the whole document ---	1-21
Y	WO,A,92 03463 (SANDOZ LTD.) 5 March 1992 see abstract ---	1-21
Y	EP,A,0 423 777 (G.D.SEARLE AND CO.) 24 April 1991 see page 2, line 1 - page 6, line 47 ---	1-21
Y	WO,A,89 08658 (SCRIPPS CLINIC AND RESEARCH FOUNDATION) 21 September 1989 see the whole document ---	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1994	15. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scott, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF MEDICINAL CHEMISTRY vol. 33, no. 7 , July 1990 , WASHINGTON US pages 1919 - 1924 A.J.HUTCHISON ET AL. '2-(Arylalkylamino)ad enosin-5'-uronamides: A New Class of Highly Selective Adenosine A2 Receptor Ligands.' see the whole document	1-21

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INTERNATIONAL SEARCH REPORT

[redacted] Application No.
PCT/EP 94/ 00145

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

NATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 94/00145

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		JP-A-	63201196	19-08-88
		US-A-	4968697	06-11-90
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		JP-A-	3145423	20-06-91
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		AU-A-	3410589	05-10-89
		EP-A-	0364559	25-04-90
		JP-T-	3501258	22-03-91
		US-A-	5106837	21-04-92